

Functional Imaging Investigation of Psychedelic Visual Imagery

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2019

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This thesis is submitted for the degree of Doctor of Philosophy (Ph.D)

Supervised by Robin Carhart-Harris, Robert Leech and David Nutt

Dedicated with love to Nameri who transformed into Emanu during the writing of
this thesis, and to my beloved Noa who gave him life

מוקדש באהבה לנמרי אשר הפך לעימנו בזמן כתיבת התיזה, ולנועה אהובתי אשר העניקה לו חיים

Viva Famila

Tiger got to hunt,
Bird got to fly;
Man got to sit and wonder 'why, why, why?'
Tiger got to sleep,
Bird got to land;
Man got to tell himself he understand

— The Books of Bokonon

“Don’t try to make ice-cubes out of a flowing river”

— Laura Huxley

Acknowledgements

I would like to acknowledge all information sources which are hard to pinpoint. These include books, papers, posters, the World Wide Web and especially Wikipedia, visions, films, TV series, the news, personal intuition, music, collective knowledge, culture, and most importantly interpersonal communications.

I would like to acknowledge my privileges: Man, White, Wealthy, Healthy and surrounded by Lovely Loving people. It would have been a rougher ride without these.

I would like to acknowledge Caffeine, mainly in the form of double espresso, which served as an irreplaceable ally in the process of writing this thesis.

I would like to acknowledge Imperial College President's PhD Scholarship Scheme for funding my PhD, Albert Hobohm who his generous donation aided me in finalizing the thesis, and the Beckley Foundation and Walcea.com crowdfunding campaign which funded the research presented in this thesis.

I would like to acknowledge [SCONUL Access](#), for allowing to explore many other libraries during my thesis writing. Out of all libraries, a special thanks to University College London (UCL) main library, where most of the writing of this thesis took place - where I consolidated knowledge, and transformed into an expert. Synchronistically, at the hospital on the other side of the road (UCLH), pretty much in the same period, Noa (my wife) has consolidated life and we transformed into parents. Baby and thesis in a condensed period of creation.

I would like to acknowledge my teachers within the academia. Csaba Orban, whom patiently and passionately thought me the secrets of bash and fMRI and more importantly how to support a colleague-friend - without wanting anything in return; Marty Sereno, for the long detailed conversations and for the huge trust - a true model of compassionate wisdom; Rob Leech for the lightness in supervision and the anti-establishment vibes; David Nutt for permitting and empowering; and Robin Carhart-Harris for being the best boss-friend ever, for welcoming, trusting, allowing, gently directing, editing, and listening.

I would like to acknowledge the rest of the psychedelic research group (PRG). Particularly Mendel Kaelen (woof woof), Chris Timmermann, Ros Watts and David Erritzoe, for passionate brainstorming, sharing beauty and being playful. Also to Luke Williams, Eduardo Schenberg, Taylor Lyons, Tobias Buchborn, Bruna Giribaldi, Eline Haijen, Hannes Kettner, Hannah Douglass, Laura Kaertner, Melissa Shukuroglou, Jonny Martell, Lisa Luan, Midge Baker Jones, Lea Mertens, and Shima Espahbodi. It feels great to belong to such a proud and smiley group of people, and it is a true privilege to have deep connections with “colleagues”.

I would like to acknowledge Oliver Sacks that sparked me into neuroscience with “*The man who mistook his wife for a hat*”, and approved my venture into psychedelic science with his synchronized publication of *Hallucinations* (2012). Oliver directed many to become neuroscientists/neurologists and he has done this by being deeply humane while discussing with fascination the technicalities of the brain. May his compassion and curiosity linger in any neuroscientist he moved. The font used for this thesis, *Trump Mediaeval*, was used in Oliver’s *Hallucinations*.

I would like to acknowledge Romy Lorenz. Her PhD Thesis’s acknowledgments section made me cry and revealed me how beautiful (and fun) this section can be.

I would like to acknowledge my parents and their partners for unconditional love, for conditional love, and for some financial support when needed.

I would like to acknowledge Adi, my sister. Her absence is my life force.

I would like to acknowledge Noa, my beloved, who exercised loving altruism that allowed me to peruse my passion. Who is my best supporter and critic, and for grounding me when I fly too high.

I would like to acknowledge Emanu, our baby boy, for the future – where purpose [is](#). “We are an old family; We are a new family; We are the same family stronger than before; We honor you; We empower you; To be who you are.”

“*Gratitude is Heaven itself*” – William Blake

Copyright Declaration

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Statement of Publications

Parts of this thesis have been published in different journals. Parts of chapter 3 has been published in *PNAS* (Carhart-Harris et al. 2016). Parts of chapter 4 has been published in *Human Brain Mapping* (Roseman et al. 2016). Parts of section 1.7 has been published in *Frontiers in pharmacology* (Roseman et al. 2017).

Carhart-Harris, R. L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., ... & Nutt, D. J. (2016). Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proceedings of the National Academy of Sciences*, 113(17), 4853-4858.

Roseman, L., Sereno, M. I., Leech, R., Kaelen, M., Orban, C., McGonigle, J., ... & Carhart-Harris, R. L. (2016). LSD alters eyes-closed functional connectivity within the early visual cortex in a retinotopic fashion. *Human brain mapping*, 37(8), 3031-3040.

Roseman, L., Nutt, D. J., & Carhart-Harris, R. L. (2017). Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. *Frontiers in pharmacology*, 8, 974.

Statement of Originality

For the LSD data presented in chapters 3 and 4, the study design, recruitment of participants and fMRI scanning were performed by Robin Carhart-Harris, Mendel Kaelen, Mark Bolstridge, Suresh Muthukumaraswamy, Tim Williams and Wouter Droog, and was supervised by David Nutt and Robin Carhart-Harris. The pipeline that was used for fMRI preprocessing was developed by Csaba Orban and John McGonigle, and adapted by myself. MEG data in chapter 3 was preprocessed by Suresh Muthukumaraswamy, Eduardo Schenberg and Mednel Kaelen, the rest of the MEG analysis presented in this chapter has been conducted by myself. I declare that all other work contained within this thesis is my own, unless otherwise stated, and conforms to the rules and guidelines set out by Imperial College London.

For the psilocybin data presented in chapters 3 and 5, the study design, recruitment of participants and fMRI scanning were performed by Robin Carhart-Harris, David Erritzoe, and Tim Williams, and was supervised by David Nutt and Robin Carhart-Harris. The rest of the fMRI analysis was conducted by myself.

The research in this thesis received financial and intellectual support from the Beckley Foundation and was conducted as part of a wider Beckley-Imperial research programme (Principle investigators: David Nutt and Robin Carhart-Harris).

Robin Carhart-Harris, David Nutt and Robert Leech supervised this thesis.

Funding

My PhD was funded by Imperial College President's PhD Scholarship. The last months of my PhD were generously funded by Albert Hobohm. The LSD research presented in this thesis was funded by the Beckley Foundation and [Walacea.com](https://www.walacea.com) crowdfunding campaign. The psilocybin research presented in this thesis was funded by Beckley Foundation, Neuropsychoanalysis Foundation, Multidisciplinary Association for Psychedelic Studies (MAPS), and the Heffter Research Institute.

Abbreviations

2C-B	2,5-dimethoxy-4-bromophenethylamine
5-HT _{2A} R	Serotonin 2A Receptor
5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine
ACC	Anterior Cingulate Cortex
AFNI	Analysis of Functional NeuroImages
ANTS	Advanced Normalization Tools
ASC	Altered State of Consciousness
ASL	Arterial Spin Labeling
AUA	Auditory Alterations
BOLD	Blood-Oxygen-Level Dependent
CBF	Cerebral Blood Flow
CSF	Cerebrospinal Fluid
CSTC	Cortico-Striato-Thalamic-Cortical
DED	Dread of Ego Dissolution
DMN	Default Mode Network
DMT	Dimethyltryptamine
DV	Draining Vein
ECG	Electrocardiogram
EEG	Electroencephalography
EPSC	Excitatory Postsynaptic Current
ERG	Electroretinogram
FD	Frame-wise Displacement
FDA	Food and Drug Administration
FFA	Fusiform Face Area
fMRI	Functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
FWHM	Full Width at Half-Maximum
GCPR	G Protein-Coupled Receptor
GLM	General Linear Model
GM	Grey Matter
HRF	Hemodynamic Response Function
ICA	Independent Component Analysis
IFG	Inferior Frontal Gyrus
ISC	Inter-Subject Synchronization
IV	Intravenous
LGN	Lateral Geniculate Nucleus

LSA	d-Lysergic acid amide
LSD	Lysergic acid diethylamide
MAOI	Monoamine Oxidase Inhibitors
MCC	Mid-Cingulate Cortex
MEG	Magnetoencephalography
MEQ	Mystical Experience Questionnaire
MFG	Middle Frontal Gyrus
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic acid
MT	Middle Temporal (V5)
NHS	National Health Service
OBN	Oceanic Boundlessness
PCR	Polymerase Chain Reaction
PDD	Parkinson's Disease Dementia
PET	Positron-Emission Tomography
PFC	Prefrontal Cortex
PGO	Ponto-Geniculo-Occipital
RC	Retinotopic Coordination
REM	Repetitive Eye Movement
RF	Radio Frequency
ROI	Region Of Interest
RSFC	Resting State Functional Connectivity
RSN	Resting State Network
rTMS	Repetitive Transcranial Magnetic Stimulation
SD	Standard Deviation
TE	Echo Time
TFCE	Threshold Free Cluster Enhancement
THH	Tetrahydroharmine
TMS	Transcranial Magnetic Stimulation
TR	Repetition Time
V1	Primary Visual Cortex
V2	Secondary Visual Cortex
V3	Third Visual Cortex
VAS	Visual Analogue Scale
VIR	Vigilance Reduction
VRS	Visionary Restructuralization
WM	White Matter

Abstract

Psychedelics can induce eyes-closed imagery in which various visions can be experienced. These visions vary from simple geometrical patterns, to more complex imagery, to full immersion within “other realms”. Past studies suggest that the visual cortex is involved in processing these visions, yet these studies were limited into investigation of activity. In this thesis, the aim was to expand on the involvement of the visual cortex by investigating processes that are beyond simple activation maps, such as functional connectivity and dynamics.

In study 1, it was hypothesized that the visual cortex will show increased functional connectivity with many cortical and subcortical regions. This was investigated with 15 subjects that were scanned using fMRI under the influence of 75 µg of LSD or placebo. The results of this study showed increased resting state functional connectivity (RSFC) between the primary visual cortex and many cortical and subcortical regions. This result correlated with subjective ratings of psychedelic imagery and with occipital alpha power suppression measured with MEG, which is a reliable neural correlate of the intensity of the psychedelic state.

In study 2, it was hypothesized that connectivity within the visual cortex would match its retinotopic architecture. Retinotopic mapping is the representation of the visual field (the world we observe) in the visual cortex – e.g. areas which are near to each other in the visual field will be near each other in the visual cortex. In this study, it was found that under LSD (same procedure as study 1), with eyes closed, connectivity patterns between different subregions of the visual cortex matched the retinotopic mapping of these regions, suggesting that the visual system behaves as if it is seeing spatially localized input, with eyes-closed under LSD.

In study 3, it was hypothesized that during the onset phase of psychedelic imagery, the activation of subregions of the visual cortex will be from low level to high level areas, which is according to the subjective dynamics of the experience – i.e. from simple to complex. This was tested in 9 subjects that were scanned in the fMRI during the onset or “come-up” phase - i.e. 3 minutes post (1 min) infusion of 2mg psilocybin IV - which has a particularly fast onset. Results in this study revealed that during the onset phase the BOLD dynamics of regions within the ventral stream are organized by the hierarchy of regions.

Overall, study 1 and 2 revealed that, with eyes closed, under LSD, communication patterns between visual cortex and the rest of the brain and within the visual cortex match the kind of processing known to occur during regular vision. This adds to a body of knowledge supporting the view that the visual cortex is particularly engaged under the influence of psychedelics, and by measuring patterns of connectivity, we were able to provide strong support for the view that abnormal activity in the visual cortex underlies psychedelic imagery.

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1. BACKGROUND

“In this liminal condition, the neophyte shaman becomes vulnerable and receptive to communication with spirits and animals. This is 'the kiss of knowledge,' the experience of intimacy with the nonhuman world. Such communion with plants, creatures, geographical features, and the unseen can involve language or be beyond words altogether.”

— Joan Halifax

1.1 Forward

Psychedelic - from Ancient Greek *psukhê*, “mind, soul” + *dêlos*, “manifest, visible”

Psychedelics are a class of drugs that have been used throughout history in many ways. The multidisciplinary appeal of psychedelics is evident when considering the many practices they interact with: **shamanism** (Campos, 2011; Labate and Jungaberle, 2011; Shanon, 2002a; Winkelman, 2010), **science** (Carhart-Harris, et al., 2014; Hofmann, 1979; Kent, 2010; Langlitz, 2007; Lilly, 1972; Shanon, 2002a; Shulgin and Shulgin, 1990; Strassman, 2000), **therapy** (Cohen, 1964; Fadiman, 2011; Fisher, 2015; Grof, 1975; Grof, et al., 1980; Richards, 2015; Stolaroff, 2004), **philosophy** (Huxley, 1954; Huxley, 1962; Huxley, 1977; McKenna, 1999), **visionary art** (Grey, 1990; Luna and Amaringo, 1991; Mikosz, 2015), **mind exploration (psychonauts)** (St John, 2015), **festivals** (St John, 2008; Wolfe, 1968), **counter culture** (Lee and Shlain, 1985; McKenna, 1999; Wolfe, 1968), **CIA experiments** (Lee and Shlain, 1985), **modern psychedelic ceremonies** (Vayne, 2017), and **much more**.

The field of psychedelic research is experiencing a renaissance (Sessa, 2012), and I’m fortunate to be part of it. I have decided to focus in this thesis on psychedelic imagery, though I find other aspects of the psychedelic experience fascinating as well. The scientific literature on the visual cortex is arguably more robust than for any other brain region, and therefore the visual cortex can be investigated with more certainty and with the hope that findings in the visual cortex will serve as a model for understanding higher level processing as well. My choice of centering my thesis on the visual cortex, and specifically on the primary visual cortex, resonates well with Hubel’s sentiments: “*[...] knowing that one part of the cortex works in a rational, easily understood way gives grounds for optimism that other areas will too*” (Hubel, 1988).

1.2 Other Names for Psychedelics

Phantastica, 1924, *imaginary*. Coined by Louis Lewin. Lewin classed 5 categories of drugs: Inebriantia (Inebriants), Exitantia (Stimulants), Euphorica (Euphorians), Hypnotica (Tranquilizers), and Phantastica.

Hallucinogen, 1950-1955, *hallucination producer*. Coined by Abram Hoffer and Humphry Osmond (who also coined *Psychedelic* later on). Sir Thomas Browne in 1646 coined the term '*hallucination*' from the Latin word "alucinari" meaning "to wander in the mind".

Psycholytic, 1955, *mind loosening*. A name given by Ronald Sandison to describe therapy with low to medium doses of psychedelics.

Psychotomimetic, 1956: *mimicking psychosis*. Coined by neurophysiologist Ralph Gerard (Gerard, 1956). Similar terms from the same period are Schizogens, Psychotica and Psychotogens.

Phanerothyme, 1956, *spirit-manifest*. Suggested by Aldous Huxley in a letter to Humphry Osmond: "To make this mundane world sublime, take half a gram of phanerothyme".

Psychedelic, 1956, *mind-manifest*. Coined by Humphry Osmond in a response letter to Aldous Huxley: "To fathom Hell or soar angelic, just take a pinch of psychedelic".

Entheogen, 1979, *divine producer*. Coined by a group of ethnobotanists and scholars of mythology (Carl Ruck, Jeremy Bigwood, Danny Staples, Richard Evans Schultes, Jonathan Ott and Gordon Wasson).

Necrotogen, *near-death producer*. Suggested by Rupert Sheldrake to Terence McKenna.

Psychointegrator, 1995, *integrating psyche*. Suggested by Michael Winkelmann

Sacred Medicines / Sacred Plants / Plant Medicines / Plant Teachers. Terms that are in use for shamanic, neo-shamanic, and other ritualistic contexts.

The following segment is from a conversation between Osmond, Rinkel and Gerard, in "Neuropharmacology: Transactions of the Second Conference, May 25, 26, and 27, 1955, Princeton, NJ" (Rinkel, 1956):

***Rinkel:** I would like to bring up a controversial matter which is very much on my mind. We are dealing here with chemicals – mesacrine, LSD, and other chemicals that Dr. Osmond mentioned earlier as affecting behavior – and we are groping for a name. Repeatedly, the name of "Phantastica" came up. Dr. Becker did not like this name for LSD, and he called it a "psychoticum". Dr. Gerard speaks of "psychosomimetic" drugs. Dr Osmond and Dr Hoffer coined the word "hallucinogens", and they defined it as a group of compounds causing hallucinations and having an indole ring in common.*

***Osmond:** I think we would probably like to withdraw that now."*

Osmond coined the term *hallucinogen*, then withdrew and coined *psychedelic*. There are two problems with the term *hallucinogen*. The first is that it suggests that the visual elements are central to this class of drugs. This position now seems untenable because other psychological components appear to be at least as pronounced. The second problem is that hallucinations, by definition, seem real to the experiencer and should have qualities of ordinary visual perception. Contrastingly, the visionary elements of psychedelics are usually quite different to the visual perception of everyday reality and some prefer to call them pseudo-hallucinations, as users, in most

cases, know how to differentiate between the psychedelic imagery and everyday reality.

The criticism towards the term *psychedelic* (mind-manifesting) comes from shamanic and religious models in which one believes that experiencing a different reality, or experiencing a mystical-type experience reveals truths which are beyond the subjective mind of the user.

Grof defined psychedelics as nonspecific amplifiers (Grof, et al., 1980), a term which reveals why it is challenging to narrow them down to one name, as they might amplify many functions of the human mind.

1.3 Safety

Compared with other drugs of potential misuse, the harm potential of psychedelics is generally considered to be relatively low (Cohen, 1967; Krebs and Johansen, 2013; Nutt, et al., 2010) and they rarely lead to addiction or dependency (O'Brien, 1996). Yet, it is important to note safety guidelines for psychedelic research that could minimize harm within the lab setting and prevent prolonged psychosis. These guidelines are taken from Johnson, et al. (2008), which is an essential read for any researcher planning to conduct a psychedelic study. Johnson constructed his guidelines based on both a 50 years old tradition of psychedelic therapy (Dyck, 2006; Eisner and Cohen, 1958; Grof, et al., 1980; Pahnke, et al., 1969; Passie, 1997; Richards, 2015), and old indigenous traditions which utilized psychedelics for healing and ceremonial purposes (Harner, 1972; Labate and Cavnar, 2014; Lowy, 1971; Reichel-Dolmatoff, 1975; Schultes, 1969; Schultes and Hofmann, 1979; Winkelman, 2010).

Presented below is a summary of Johnson's general guidelines for safe psychedelic research: 1) Selection of volunteers should include people in good general health who have passed psychiatric screening criteria that is relevant for the study. 2)

Interpersonal relationship with researchers and additional study personal should be warm and friendly. Researchers should do what is needed to stay centered during the day in order to have full attention to the subject and his needs and maintain a positive social rapport. Importantly, “investigators should work with all personnel that the volunteer may encounter (e.g. receptionist, building security, nurses) to ensure that volunteers are treated with courtesy and respect”. 3) The environment should be safe as the subject might be distorted. Furthermore, aesthetically pleasing and comfortable environment - which is warmer than regular clinical environment - is essential for subject’s wellbeing and stress reduction. 4) Preparation meetings with volunteers to inform them in details about the study, the possible experiences that might occur, and to build rapport and trust with the researchers, are important for a safe experience.

1.4 Visual Cortex

1.4.1 Hierarchy of Visual Cortex

The visual system is organized in a hierarchical fashion. The eyes send information to lateral geniculate nucleus (LGN) in the thalamus, from LGN to cortical layer IV in V1, and from V1 to other higher level visual sub-regions (V2, V3, V4, MT, etc.), which process, in parallel fashion, different features of the visual information (color, movement, etc.) (Figure 1.1). V1 receives the most “raw” visual input and therefore has the highest spatial resolution of this visual information. As a general rule, as information processing progresses up in the visual hierarchy, abstraction and interpretation increases while spatial resolution decreases. It is important to note that the visual “hierarchy” is not entirely rigid, and there are other secondary visual pathways, feedback loops, and lateral connections between all regions (e.g most of the input to LGN comes not from the retina, but from V1 feedback) (Stone, 2012).

1.4.2 Retinotopic Organization

The visual field is retinotopically re-represented several times in subregions of the occipital cortex (Hubel and Wiesel, 1977; Hubel and Livingstone, 1987; Zeki, 1978). Retinotopic (or topological) organization means that nearby regions in the retina project to nearby cortical regions - neighboring cells in the cortex will have receptive fields close to each other in the visual fields (Tootell, et al., 1988) (Figure 1.2). By presenting videos of rotating wedges or expanding rings it is possible to map brain areas that show activity that is dependent on the spatial location of the stimulus. This technique has helped identify the borders between neighboring visual regions (e.g. V1, V2, V3) (Serenio, et al., 1995) (Figure 1.3). Regarding the resting state activity of the visual cortex, it is suggested that spontaneous activity in the visual cortex spreads through the visual hierarchy in a retinotopic manner (Kenet, et al., 2003). Moreover, given the involvement of retinotopically-sensitive regions in the processing of spatial information, studying their spontaneous activity during resting-state conditions, with and without psychedelics, may produce insights into how visual neural systems underlie the emergence of psychedelic imagery.

1.4.3 Parvocellular vs. Magnocellular Pathways

The visual cortex is separated to parvocellular (ventral) and magnocellular (dorsal) streams (Figure 1.4) (Schneider, 1969). The separation into parvocellular stream (to temporal cortex) and magnocellular stream (to parietal cortex) begins already in the retina (Baizer, et al., 1991), continues to LGN, to V1 and from there to ventral and dorsal streams. There are two photoreceptors in the retina, the cones and the rods. The cones are foveal, process high-light vision, color sensitive, and with high spatial resolution. The rods are peripheral, process low-light vision, color insensitive, and with low spatial resolution. In the LGN, the 4 *parvocellular* layers receive input mainly from cones (foveal), and the 2 *magnocellular* layers receive input mainly from rods (peripheral). In V1, layer 4C β receive input from parvocellular LGN, and layer 4C α from magnocellular LGN. Two processing stream continue from V1 and these are known as the ventral stream (parvocellular) and the dorsal stream (magnocellular) (Livingstone and Hubel, 1988; Schneider, 1969). The parvocellular stream, which

continues to temporal areas, is also called the “what” pathway. It is color sensitive, stationary, with high spatial resolution (like the cones), and specifies in processing shapes, properties of shapes, and identification. The magnocellular stream, which continues to parietal areas, is also called the “where” pathway. It is insensitive to color, transient, with low spatial resolution (like the rods), and specifies in processing movement, location and spatial relations (Hubel, 1988). Schneider (1969) suggested that there are actually two visual systems and it is intriguing to speculate how they may differ in relation to psychedelic imagery.

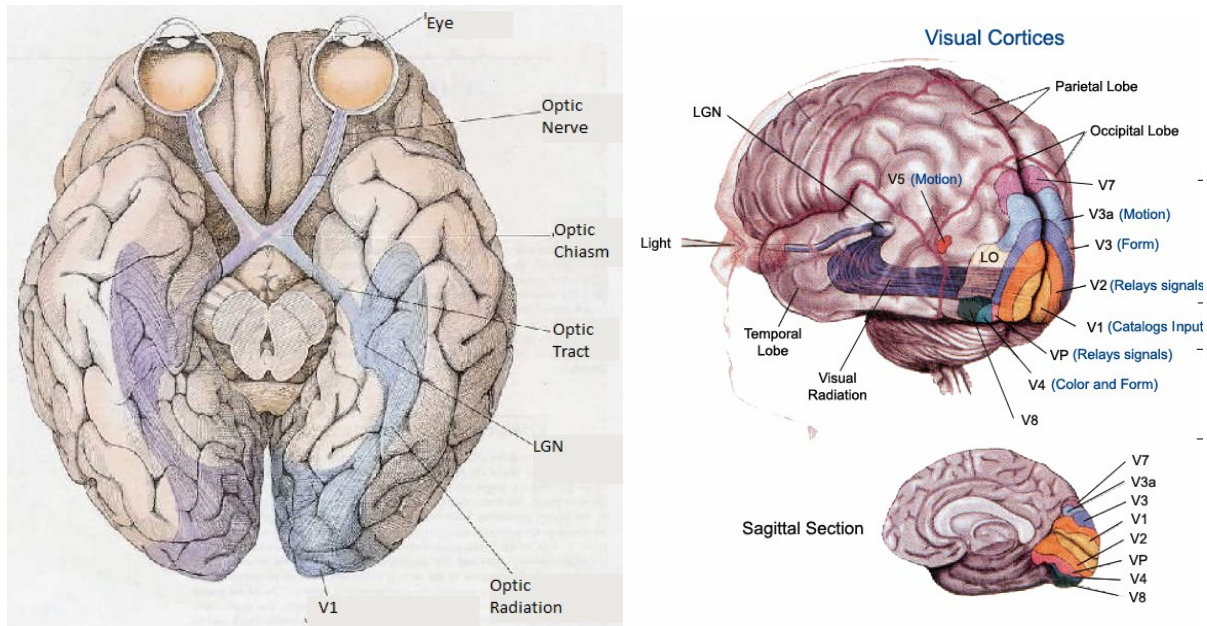


Figure 1.1. Visual Hierarchy

Left: from Hubel (1988). The visual pathway, from the eyes to primary visual cortex, of a human brain, as seen from below. *Right:* By Terese Winslow (1999). Functional subdivision of the visual cortex.

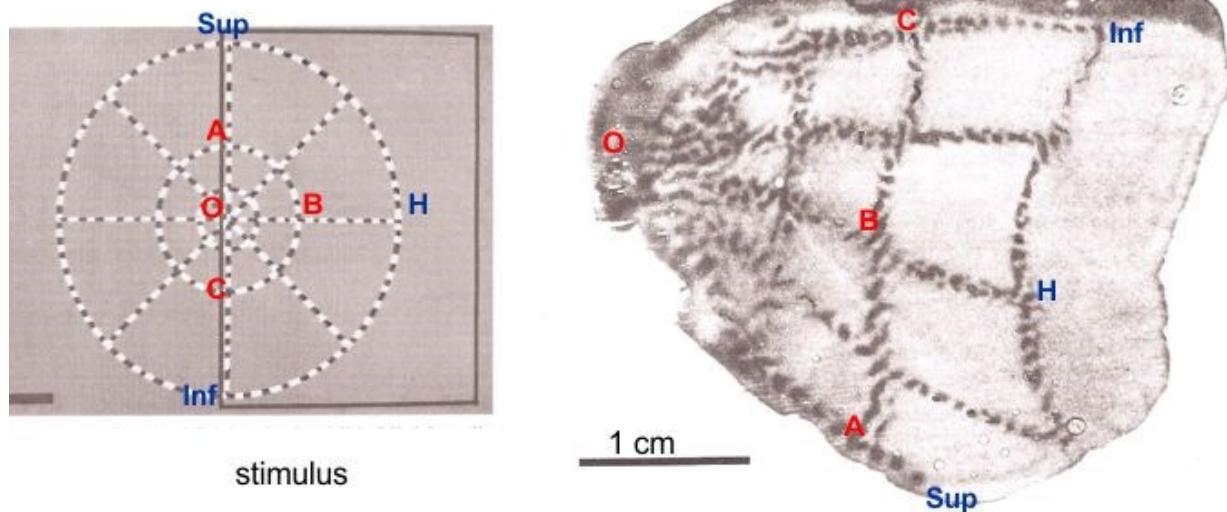


Figure 1.2. Macaque Retinotopic Mapping

From Tootell, et al. (1988), reproduced with permission. The stimulus on the left was presented to a macaque monkey after injection of radioactive glucose. The monkey was sacrificed after staring at the stimulus. The right figure shows the radioactive labelling on the flattened left V1 of the macaque monkey. A pattern of activation in the cortex that corresponds to the stimulus is observed clearly. Polar angles in the stimulus are the horizontal lines on the cortex, and rings are the vertical lines on the cortex. Foveal areas are in the posterior part of the cortex (o) and peripheral areas are anterior. Retinotopic mapping is the transformation from the visual field to the cortex.

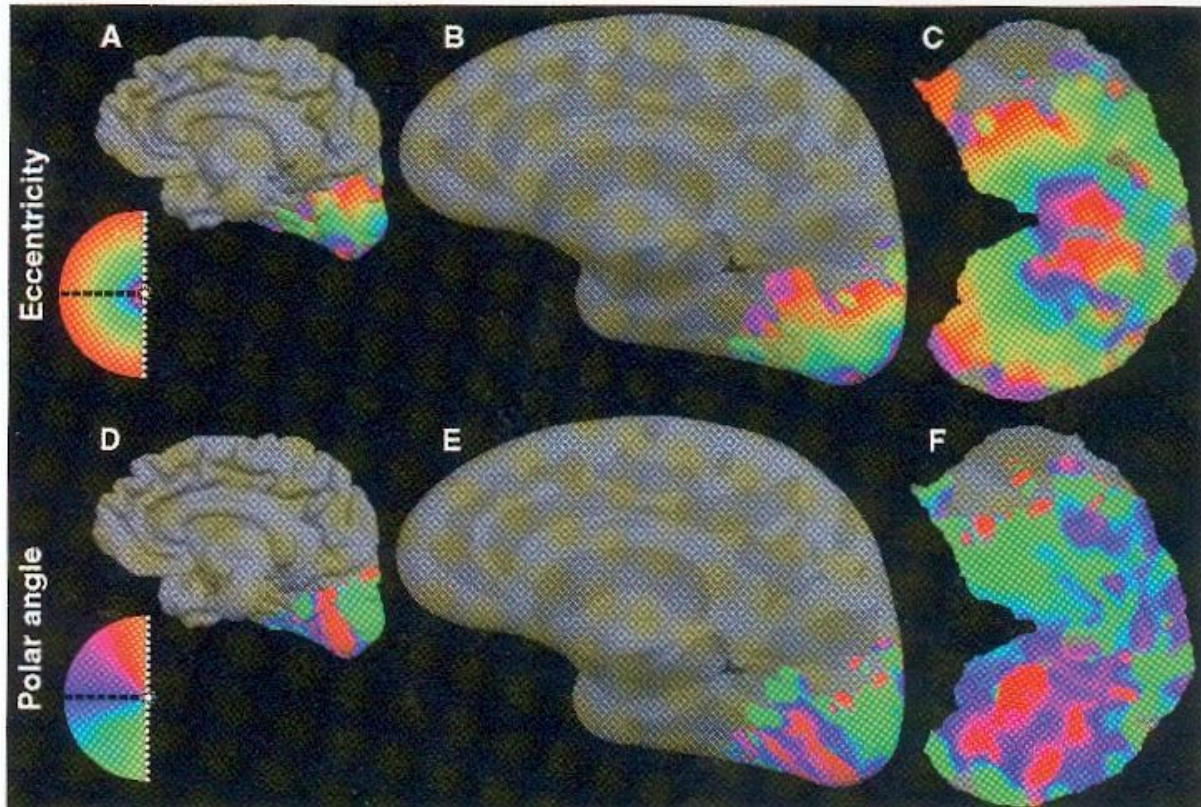


Figure 1.3. Human Retinotopic mapping

From Sereno, et al. (1995), reproduced with permission. Retinotopic maps of eccentricity rings (top) and polar angles (bottom) presented on the folded (left), inflated (center) and flattened (right) cortex of a human subject. Expanding rings (eccentricity), and rotating wedges (polar) were presented to subjects in the fMRI and activity that corresponds to the rings and wedges was recorded. The location of the rings and wedges is presented at the left. On the top eccentricity map, the gradient moves from occipital to anterior areas based on eccentricity (foveal, in red+purple, is most occipital; peripheral, in red, is most anterior). On the bottom polar angle maps, blue represents the horizontal meridian, and orange and green the vertical meridian (top and bottom respectively). Each sub-region of the visual cortex has a retinotopic mapping of the visual field, and therefore, the activity that corresponds to the stimuli appears in many cortical areas. The borders between cortical areas are vertical and horizontal meridians.

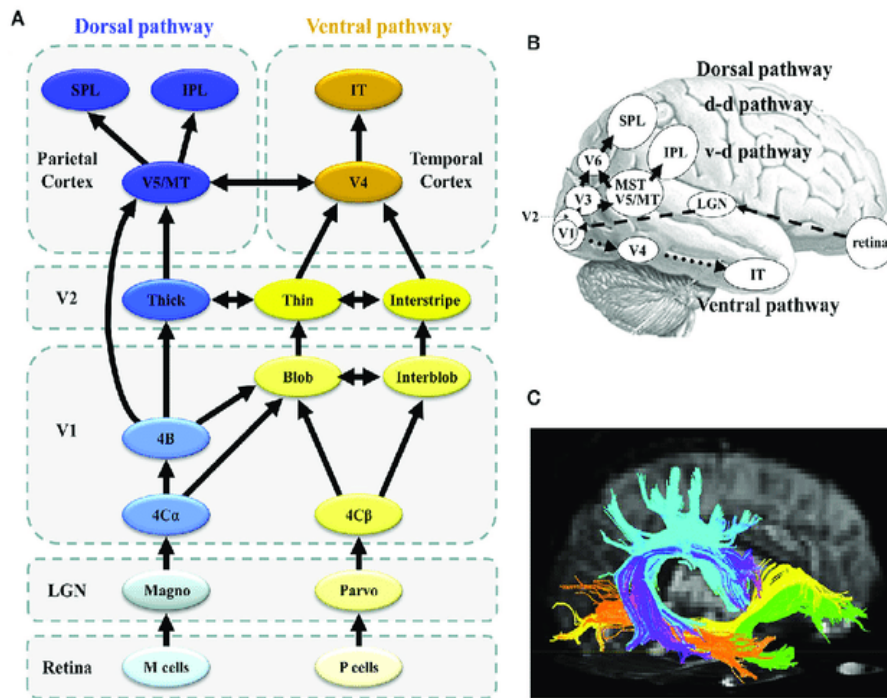


Figure 1.4. Magnocellular vs. Parvocellular Streams

From Yamasaki, et al. (2017), reproduced without need for permission. (A) The monkey visual system is characterized by a set of parallel, hierarchical, multistage systems. There are two major parallel streams: parvocellular (or ventral, or “what” stream) and magnocellular (or dorsal, or “where” stream) pathways. (B) The human visual system is analogous to that of the monkey. Two major parallel streams are present. (C) From (Jang, 2013). The ventral stream in orange and yellow, while the dorsal stream is sky-blue. Most of the retinal cells in the parvocellular stream are P cells which are mainly cones (high-light vision, foveal, color sensitive, and high spatial acuity), and most retinal cells in the magnocellular stream are M cells which are mainly rods (low-light vision, peripheral, no color vision, and low spatial acuity). The magnocellular stream processes information about location and movement. The parvocellular stream processes shapes, properties of shapes, and identity.

d-d pathway, dorso-dorsal pathway; v-d pathway, ventro-dorsal pathway; LGN, lateral geniculate nucleus; MT, middle temporal area; MST, medial superior temporal area; IPL, inferior parietal lobule, SPL, superior parietal lobule; IT, inferior temporal cortex;

SLF, superior longitudinal fasciculus, IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus.

1.5 Classic Psychedelics - Basics

1.5.1 Background

Since the discovery of LSD, in 1943 by Albert Hofmann (Hofmann, 1979), classic psychedelics were researched for a period spanning three decades with more than 1000 clinical papers published discussing 40,000 patients (Grinspoon and Bakalar, 1979). However, by the end of the 60's psychedelics had been ostracized from science due to a cultural and political backlash (Baum, 2016; Grinspoon and Bakalar, 1979) likely associated with increased use of LSD, particularly among the 1960's counter-culture movement (many argue that LSD helped fuel the "counter" in counter-culture (Lee and Shlain, 1985)), and from the tightening of FDA regulations (Oram, 2012). The political backlash moved LSD and other psychedelics to schedule 1 classification in the Controlled Substances Act of 1970. This resulted in a scarcity of psychedelic research for a number of decades. After these silent decades of relatively little legal scientific investigation, we are witnessing today a gradual return of psychedelic science (Sessa, 2012). Within the academia, classic psychedelics have been and are being used to investigate psychology, culture, religion, brain and consciousness.

Classic psychedelics (Figure 1.5) (serotonergic psychedelics) are a sub category of psychedelics which are agonists of the serotonin 2A receptor (5-HT_{2A}R) (Nichols, 2016). Most of the classic psychedelics belong to one of two subcategories defined by their specific molecule structure: tryptamines and phenethylamines. Serotonin is the most known endogenous tryptamine, and dopamine, noradrenalin and adrenalin are the known endogenous phenethylamines. The common psychedelic tryptamines are LSD, LSA (found in seeds of Ololiuhqui (Morning Glory), and Hawaiian baby woodrose), psilocybin and psilocin (found in magic mushrooms), DMT (Found in many plants; used in ayahuasca, an Amazonian brew), and 5-MeO-DMT (found in the Sonoran Desert toad glands). Common psychedelic phenethylamine are mescaline

(found in Peyote and San Pedro cacti), 2C-B, and 25I-NBOMe. It is worth mentioning that Ayahuasca contains two plants, one with DMT which is a classic psychedelic, and the other with Harmine, Harmaline, and Tetrahydroharmine (THH) which are monoamine oxidase inhibitors (MAOIs) that prevent the digestion of DMT in the stomach¹.

1.5.2 Subjective Effects, Set & Setting, and Dose

Psychedelics can cause a myriad of effects which I will not list in full (Dittrich, 1998; Grof, 1975; Shanon, 2002a), and one suggestion is that psychedelics nonspecifically amplify (Grof, et al., 1980) context, which, of course, can be internal and external. Their effects can be euphoric or dysphoric, blissful or miserable, relaxing or stressful, peaceful or fearful, manic or depressive, meaningful or absurd, they can increase or decrease attention, sharpen or unfocus vision; they can be ego-dissolving or narcissism-inducing, expand or compress one's sense of time; they can be exciting or inhibiting, playfully fun or - in some rare occasions - irritably boring. On the sensory level, they can lead to increased sensitivity to all senses, to imagery of all senses, and to synesthetic effects. They can lead to visions with eyes closed that vary from flashes of light to geometrical patterns to complex imagery such as temples, cities, animals, and other beings. With high doses, one can feel as if he/she is fully transported to another realm with all of his/her senses intact and able to interact with different elements in that realm. More on psychedelic imagery is provided below (1.6).

The subjective effects of psychedelics are dose dependent (Carhart-Harris, et al., 2017; Studerus, et al., 2011), however, the context of the experience is crucial for determining drug effects (Carhart-Harris, et al., 2017; Haijen, et al., 2018; Studerus, et al., 2012). Context is classically divided into two main components: set & setting (Hartogsohn, 2016; Hartogsohn, 2017; Leary, et al., 1963). Set being the intrinsic

¹ Harmine, Harmaline and THH have their own visionary properties as well, and therefore the imagery state induced by ayahuasca is not related to DMT exclusively (Naranjo, 1974; Schenberg, et al., 2015).

context, i.e. personality, expectations and the pre-dose mindset of the user. Setting being the external context, e.g. whether it is his/her immediate environment or the larger cultural setting (Hartogsohn, 2014; Wallace, 1959). To reach a certain effect one should take into account how set, setting and dose interact with each other. For example, a relaxed environment could mean different things to different people as one can feel safer next to other people and another prefers to be alone in nature. Few studies investigated set & setting and have found that higher readiness (willingness to “let-go”), having an intention, and a therapeutic setting, increased the likelihood of “peak” (mystical-type) experience, while less readiness, less intention, and low trust increased the likelihood of having a challenging experience (Carhart-Harris, et al., 2017) (Figure 1.6). Furthermore, subjects with higher scores on the trait measure absorption, and in a pre-dose state of emotional excitability and activity were more sensitive to overall drug effects, and subjects that received psilocybin in the PET scanner were higher in anxiety scores than without the PET scanner (Studerus, et al., 2012).

1.5.3 5-HT_{2A} Receptor

“Psychedelic” effects are mediated by activation of serotonin 2A receptor (5-HT_{2A}R) (Halberstadt, 2015). This is most evident as Ketanserin, a 5-HT_{2A} receptor antagonist, blocks most of the effects of a classic psychedelic (Kometer, et al., 2011; Quednow, et al., 2012; Vollenweider, et al., 1998; Watakabe, et al., 2008). 5-HT_{2A}R is a G protein-coupled receptor (GPCR) and it is one out of at least 14 serotonergic receptors (Glennon and Dukat, 1995). Like all GPCR, 5-HT_{2A}R has many signal pathways which are ligand dependent (“functional selectivity”). Therefore, though both serotonin and classic psychedelics bind to the 5-HT_{2A}R, they might affect it differently by activating different intracellular signal pathways (Nichols, 2016). 5-HT_{2A}R are highly expressed all over the cortex including the visual cortex (Beliveau, et al., 2017; Burnet, et al., 1995; Erritzoe, et al., 2009; Ettrup, et al., 2014; Hall, et al., 2000; Lidow, et al., 1989; López - Giménez, et al., 2001; Pazos, et al., 1987; Saulin, et

al., 2012) (Figure 1.7). Within the visual cortex, there is high expression of 5-HT_{2A}R in the primary visual cortex (V1) compared to other subregions (Beliveau, et al., 2017; Watakabe, et al., 2008; Zilles, et al., 2002) (Figure 1.8).

5-HT_{2A}R mRNA is expressed mainly on excitatory glutamatergic neurons but also lower expression is found on inhibitory neurons (Araneda and Andrade, 1991; De Almeida and Mengod, 2007; Halberstadt, 2015; Jakab and Goldman-Rakic, 2000; Mengod, et al., 2015; Santana, et al., 2004; Tanaka and North, 1993; Willins, et al., 1997). 5-HT_{2A}R binding and mRNA expression were found in all cortical layers with high expression in layer V pyramidal neurons (Andrade, 2011; Burnet, et al., 1995; De Almeida and Mengod, 2007; Lidow, et al., 1989; López-Giménez, et al., 1998; López-Giménez, et al., 2001; Pazos, et al., 1987; Watakabe, et al., 2008). However, more specifically, within V1 highest expression was found in layer IV, which is the input layer from LGN (Burnet, et al., 1995; Lidow, et al., 1989; López-Giménez, et al., 1998; López-Giménez, et al., 2001; Pazos, et al., 1987; Watakabe, et al., 2008) (Figure 1.9). Notably, three hours of monocular deprivation (covering the eye) can lead to downregulation of 5-HT_{2A}R in layer IV of V1, suggesting V1 specific expression patterns of receptor mRNA are sustained by the ongoing visual activity (Watakabe, et al., 2008), and therefore, 5-HT_{2A}R relates to primary processing of visual input.

1.5.4 General Neuropsychopharmacology

5-HT_{2A}R are widely distributed in cortical and subcortical areas, and therefore some psychedelic effects are global. Increased connectivity was observed between different networks in the brain which are usually segregated (Carhart-Harris, et al., 2016a; Müller, et al., 2018; Roseman, et al., 2014), and generally increased global connectivity (Petri, et al., 2014; Tagliazucchi, et al., 2016b) and enhanced repertoire of brain dynamics (Tagliazucchi, et al., 2014) are observed. Furthermore, decreased connectivity within networks (integrity) is detected (Carhart-Harris, et al., 2016b; Müller, et al., 2018). As within network integration decreases, so does between-

network segregation decrease. Somewhat relatedly, it is suggested that, under the influence of psychedelics, the modular structure of neural networks is decomposed, and that the brain becomes more entropic (Carhart-Harris, et al., 2014; Carhart-Harris, 2018). These whole-brain imaging results chime with the notion that the function of 5-HT_{2A}R is to induce an acute state of high plasticity and flexibility - which can aid learning, unlearning and adaptability (Carhart-Harris and Nutt, 2017). More specific regional changes are seen in the default mode network (DMN), a network which is involved in “self” related processing (Raichle, 2015). LSD, psilocybin and ayahuasca reduced the integrity of the DMN, and DMN disintegration correlated with subjective ratings of “ego-dissolution” (Carhart-Harris, et al., 2012b; Carhart-Harris, et al., 2016a; Palhano-Fontes, et al., 2015). Increased flexibility together with increased states of selflessness might be the cause of the myriad of psychedelic effects, including the heightened sensitivity to the context (Carhart-Harris, et al., 2017).

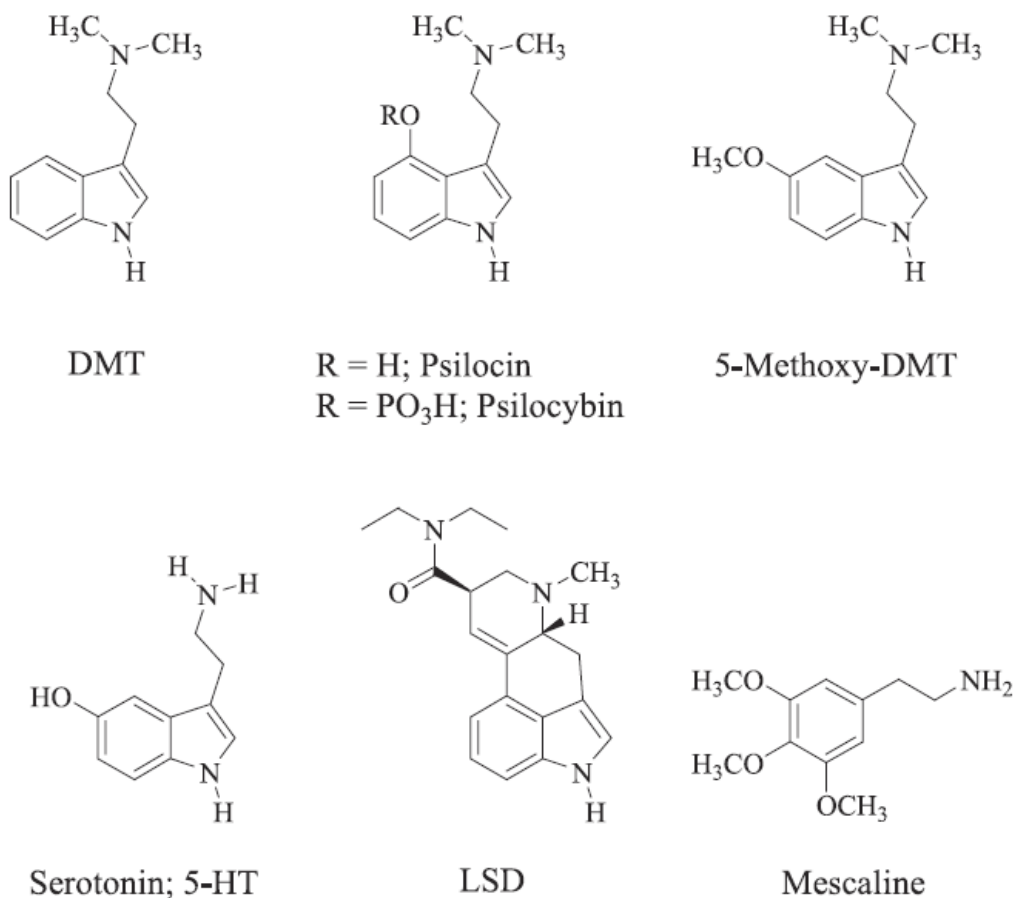


Figure 1.5. Molecular Structure of Classic Psychedelics

From Nichols (2004), reproduced with permission. Molecular structure of different psychedelics is presented. All molecules are tryptamines beside mescaline which is a phenethylamine. Serotonin (bottom, left) is an endogenous tryptamine, and other tryptamines resemble serotonin in structure.

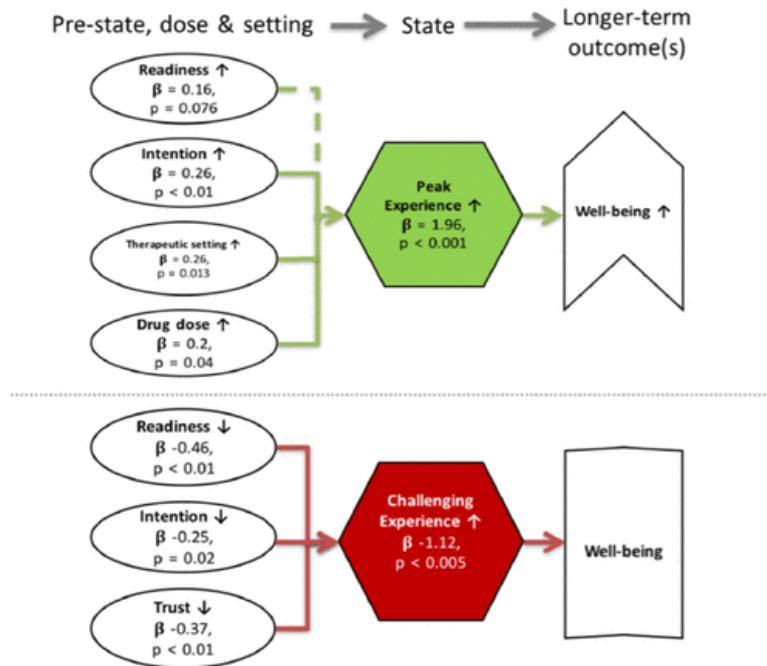


Figure 1.6. Importance of Context

From Carhart-Harris, et al. (2017), reproduced without need for permission. “Predicting a trip: Two models based on data derived from web-based survey in 266 participants who completed surveys at four key time points: (a) 1 week before; (b) 1 day before; (c) 1 day after; and (d) 2 weeks after a specific psychedelic experience. The top model shows factors predicting a ‘peak’ or ‘mystical-type’ experience under a psychedelic, which subsequently predicts improvements in psychological well-being 2 weeks later. The bottom model shows factors which (if lacking) predict a challenging psychological experience under a psychedelic, which subsequently predicts a reduced increase in psychological well-being 2 weeks later. Arrows with full lines represent significant relationships between factors and broken lines are used for trend-level relationships. Readiness contains four items such as ‘I feel ready to surrender to whatever will be’ and ‘I feel open to the upcoming experience’; intention contains two items, namely: ‘I have a clear intention for the upcoming experience’ and ‘I have strong expectations for the upcoming experience’; trust contains two items, namely: ‘I have a good feeling about my relationship with the group/people who will be with me during my experience’ and ‘I have a good relationship with the main person/people who will look after me during the upcoming experience’.”

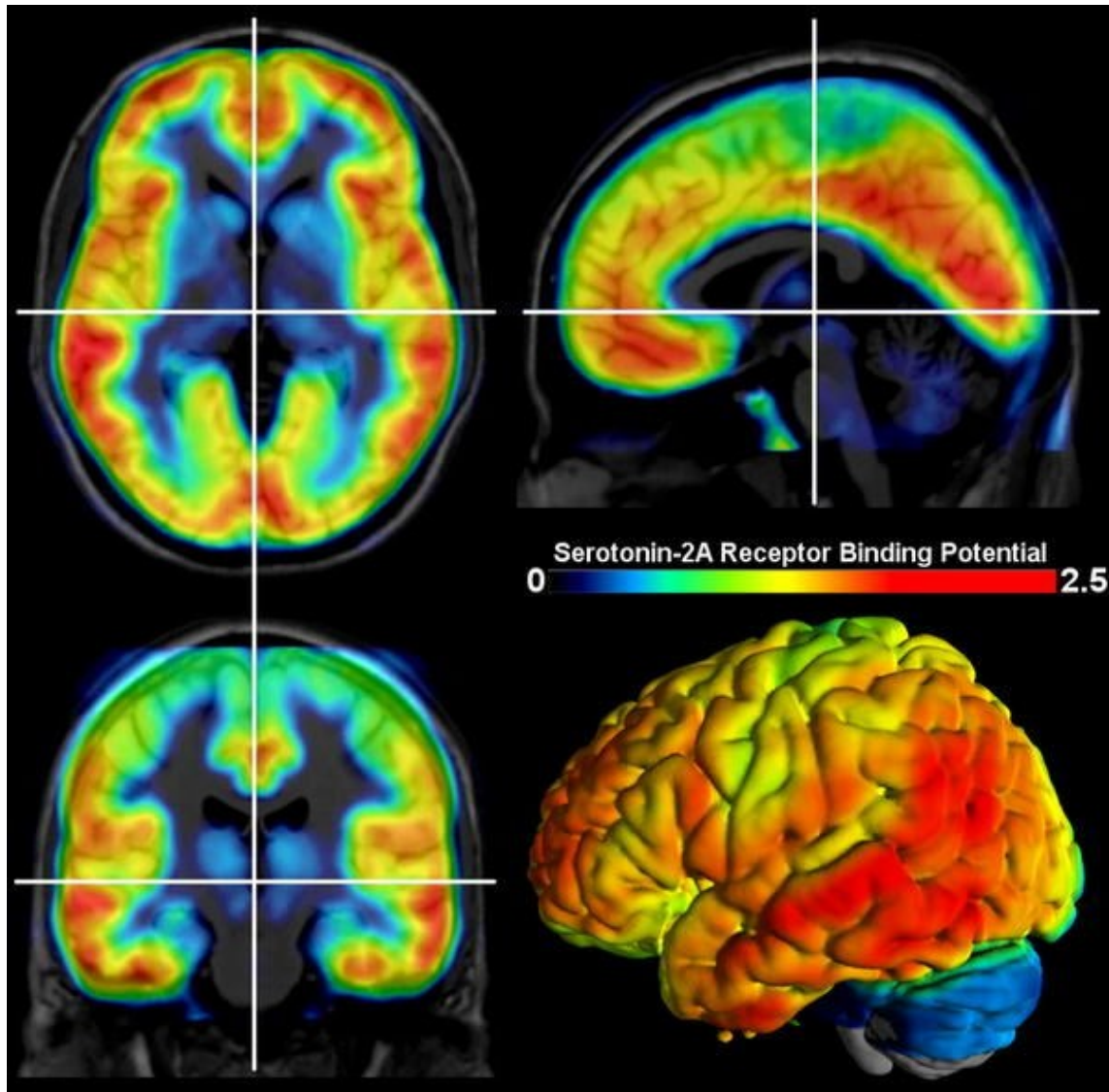


Figure 1.7. 5-HT_{2A}R Cortical Distribution

From Saulin, et al. (2012), reproduced with permission. See also Beliveau, et al. (2017). Distribution of the serotonin 2A (5-HT_{2A}) receptor in the human brain as measured with PET, using the 5-HT_{2A}-specific radioligand [18F]altanserin, based on 17 healthy subjects. Highest densities of this receptor are detected in cortical areas, especially medial frontal cortex, temporo-occipital cortex, as well as piriform and entorhinal cortex. Moderate levels are found in the limbic system and the amygdala. Very low levels of 5-HT_{2A} receptor density can be observed in the hippocampus as well as the cerebellum. Color table indicates receptor binding potentials. Maps can be downloaded from: <http://www.meduniwien.ac.at/neuroimaging/downloads.html>

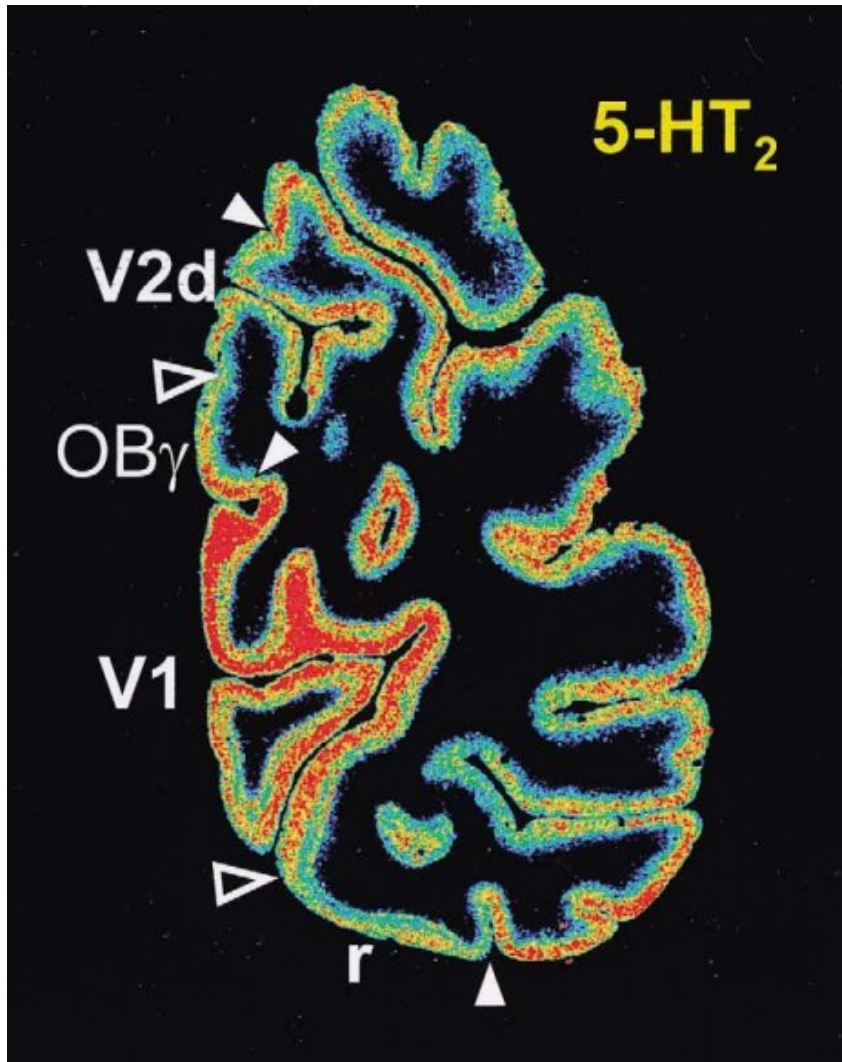


Figure 1.8. 5-HT_{2A}R in Visual cortex

From Zilles, et al. (2002), reproduced with permission. See also Beliveau, et al. (2017) and Watakabe, et al. (2008). Distribution of serotonergic 5-HT_{2A} receptors in human occipital cortex ([³H]ketanserin binding sites). The color-coding indicates receptor densities in fmol/mg protein. The filled arrowheads indicate borders of cortical areas, the white arrowhead contours indicate the borders of subareas r (rim region) within V1, and OB_γ (border tuft region) within V2. p-o, Parieto-occipital sulcus; V1, primary visual cortex; V2d, dorsal part of the secondary visual cortex; V2v, ventral part of the secondary visual cortex.

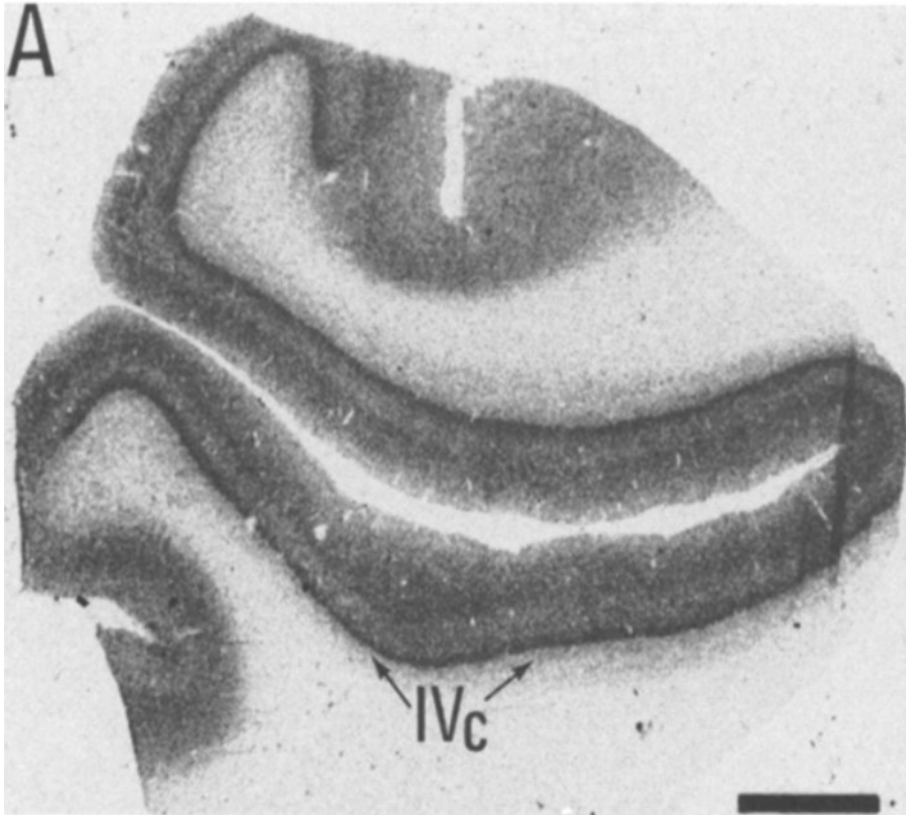


Figure 1.9. 5-HT_{2A}R Expression in V1 Layers

From Pazos, et al. (1987), reproduced with permission. Distribution of Ketanserin (5-HT_{2A} antagonist) binding in a section from a human primary visual cortex (V1). The highest densities of sites are presented over layer IVc, which receives input from the LGN, and over layer III. Average Ketanserin binding, in 8 brains, in layer IV was 293.3 ± 17.4 fmol/mg, while binding in layers V and VI was 153.8 ± 8 fmol/mg. In other cortical regions, 5-HT_{2A}R tends to be distributed in layer V.

1.6 Psychedelic Imagery – Phenomenology

“As for myself I can say for a fact that when I've taken ayahuasca I've experienced dizziness, then an aerial journey in which I recall perceiving the most gorgeous views, great cities, lofty towers, beautiful parks, and other extremely attractive objects; then I imagined myself to be alone in a forest and assaulted by a number of terrible beings from which I defended myself; thereafter I had the strong sensation of sleep.”

— Manuel Villavicencio (1858)

“I had two days spoiled by a psychological experiment with mescal, an intoxicant used by some of our Southwestern Indians in their religious ceremonies, a sort of cactus bud, of which the U. S. Government had distributed a supply to certain medical men, including Weir Mitchell, who sent me some to try. He had himself been "in fairyland." It gives the most glorious visions of color - every object thought of appears in a jeweled splendor unknown to the natural world. It disturbs the stomach somewhat, but that, according to W. M., was a cheap price, etc. I took one bud three days ago, was violently sick for 24 hours, and had no other symptom whatever except that and the Katzenjammer (hangover) the following day. I will take the visions on trust!”

— William James (1920) in a letter to his brother Henry.

For comprehensive analysis of elements of psychedelic imagery see [psychonautwiki](https://psychonautwiki.org/).

For visual representations of psychedelic imagery see *replications* in [reddit](https://www.reddit.com/r/psychonauts/).

1.6.1 The Imagery Debate

This thesis is somewhat within the context of the imagery debate (regular *imagination* which is not induced by psychedelics). For decades, there have been

scientific debates regarding imagination. On one side of the argument, the propositional theory suggests that imagination derives mainly from language, and visual areas are not necessary for imagination (Pylyshyn, 2002). On the other side of the argument, the depictive theory suggests that imagination utilize the same modalities as regular vision (Kosslyn, et al., 2006). The depictive theory does not deny any propositional properties of imagery, yet the propositional theory suggest that *only* propositional representations are used in imagery.

Within this debate, a key question is whether low-level regions of the visual system (e.g. the primary visual cortex) contribute to the representation of complex mental images (de Gelder, et al., 2014; Pearson and Kosslyn, 2015). While few decades ago, most scientists agreed that visual imagery is not recruiting the same modalities as vision (Pylyshyn, 2002), nowadays the consensus among scientists is the opposite – visual imagery is engaging the same areas as vision, including the primary visual cortex, though with lower intensity (Kosslyn, et al., 2006).

There are a few compelling studies that support the depictive theory of imagination. Visual imagery activates the primary visual cortex in a retinotopic manner based on the location of the imagery in the imagined visual field (Slotnick, et al., 2005). Furthermore, repetitive transcranial magnetic stimulation (rTMS), which is used to inhibit cortical activity, was applied on V1 while subjects were conducting an imagination task. The stimulation disrupted the subject's performance in the task, suggesting that V1 has a functional role in the performance of imagination (Kosslyn, et al., 1999). Another compelling study, showed that it is possible to decode the contents of imagination based on activity in V1, suggesting that the encoding of “quasi-pictorial” mental imagery involves V1 (Naselaris, et al., 2015).

A similar debate is whether primary visual cortex is engaged (Hong, et al., 2009; Miyauchi, et al., 2009) or disengaged (Braun, et al., 1998) during REM sleep, and there is yet any consensus in this debate. My thesis focus on a similar debate regarding

psychedelic imagery and how it incorporates the visual system: whether V1 is involved in psychedelic imagery and what the communications patterns between V1 and other regions which are related to psychedelic imagery.

1.6.2 Psychedelic Imagery vs. Imagination, Dreams and Deliriants

Psychedelic imagery occur with eyes open or closed. The term hallucinations can be quite misleading for describing psychedelic imagery as the person who experience them is usually aware that they are a result of psychedelic intake. Therefore, some prefer the term pseudo-hallucinations to describe psychedelic imagery. Furthermore, the term consensus reality – a term common among psychonauts – is used to describe everyday reality compared to psychedelic reality which some psychedelics users consider ‘real’ as well. It is quite important to differentiate between psychedelic imagery (induced by classic psychedelics), imagination, dreams, and hallucinations induced by anticholinergic deliriants (e.g scopolamine which is found in *Datura* and *Toé*) (Gyermek, 1997).

The main difference between deliriants and classic psychedelics are (Fortier, 2018): 1) Under the influence of classic psychedelics one is aware that the imagery is a result of drug intake (double bookkeeping) while with deliriants one is not always aware of the difference between imagery and consensus reality (single bookkeeping) (Shanon, 2002a). 2) With classic psychedelics one is experiencing imagery that is “out-worldly”. Many visions may differ from consensus reality (geometrical patterns, celestial cities, spirit animals, entities, angels, demons, dragons, god, gnomes and much more). However, with deliriants one usually sees mundane hallucinations that resemble objects and people from day to day life. For example, under the influence of a deliriant, Oliver Sacks “sizzled ham and eggs” for his friends, Jim and Kathy, who were not actually present with him at the moment (Sacks, 2012).

The main differences between dreaming and classic psychedelics are (Fortier, 2018): In non-lucid dreaming one is not aware to the fact that he/she is dreaming, compared

to classic psychedelics in which one is usually aware of the psychedelic intake. This difference is not relevant to lucid dreaming (a dream in which one is aware of the dreams and gains agency). In dreams, there is usually a narrative and this narrative usually relates to one's autobiography. With classic psychedelics, the narrative is looser, and sometimes abstract, and when it does exist (with high doses), it feels as if it is happening in a different realm².

The main differences between imagination and classic psychedelics are: 1) One usually has agency over imagination while one usually has less agency over psychedelic imagery (Klüver, 1928); 2) psychedelic imagery are much more vivid and stable than imagination; 3) psychedelic imagery has higher spatial resolution than imagination. This latter property might hint to the observation that while imagination is completely top down, psychedelic imagery involves both top down and bottom up processes. Up the visual cortex hierarchy, from V1 to higher-level brain regions, spatial resolution decreases while abstraction and specialization increases. When one is imagining, processing begins in the higher level areas and moves down the hierarchy back to V1. Therefore, the resolution of imagination is low because the resolution of higher-level visual areas is low (personal communication with Thomas Naselaris, Vision Sciences Society (VSS) conference (2016)). Psychedelic imagery is finely detailed, and therefore we can assume that it is not strictly top-down as imagination, but involves bottom up processes as well. 4) When imagining, one is forming an image of a specific object or figure and therefore cannot add anything new to it, as put by Sartre discussing imagination: *"I can keep looking at an image for as long as I wish: I will never find anything but what I put there"* (Sartre, 1948). To the contrary, psychedelic imagery entails novelty, and many

²more on the comparison between psychedelic state and dream state see Muzio, et al. (1966), Shanon (2002a), Carhart-Harris (2007), Kraehenmann, et al. (2017), and Tagliazucchi and Sanz (2018). Some ayahuasca shamans 'tailor' the content of their songs to their patients based on their patient's dreams in the nights previous to the ayahuasca intake (Siskind, 1973).

users are surprised to experience visions that they have never seen before (Shanon, 2002a).

One caveat to the above observations is that with very high doses of classic psychedelics and peak moments within the experience, one can be very much immersed in psychedelic reality and lose any knowledge of consensus reality, which is a state more similar to dreams and deliriums. Yet, in most cases, if asked, it is apparent that one is aware to his/her condition, and even in very intense and immersive psychedelic experiences, one can verbally report on his/her state (double bookkeeping; as seen in our group's recent DMT EEG study in which subjects managed to report intensity ratings during peak drug effects (Timmermann, et al., 2018)).

To summarize, with classic psychedelics, one can typically differentiate between imagery and consensus reality – which contrasts with dreams and the delirium experience - in which typically one cannot. Furthermore, the atmosphere and content of psychedelic imagery is qualitatively different than dreams, deliriums and imagination, as it does not resemble everyday reality. Psychedelic imagery is closer to other altered visionary states which are induced in shamanic and religious practices (e.g breathing techniques, dancing techniques, fasting), meditation, sleep deprivation, sensory deprivation/overstimulation, and spontaneously. These states are considered a different mode of experiencing the world which shares some similar aspects to dreams, imagination and hallucinations but is overall different both phenomenologically and biologically (Winkelman, 1995; Winkelman, 2010). Unlike dreams, imagination and hallucinations, the content of psychedelic imagery is usually very different to the experience of consensus reality and is generally accompanied by a sense of other worldliness (Fortier, 2018).

In this thesis the focus was of eyes-closed psychedelic imagery. The reason to focus on eyes-closed and not eyes-open was that the interest of the thesis was of 'internal'

imagery which is more prominent with eyes closed. Though this ‘internal’ imagery might also occur with high doses with eyes open, the eyes-open imagery is more related to modification of visual input from the eyes, and not to ‘internal’ creation of ‘something from nothing’ which I find to be the more interesting part of psychedelic imagery.

1.6.3 Psychedelic Visionary Art

Psychedelic imagery vary from basic geometric patterns (simple imagery) (Klüver, 1942) to more complex imagery. Many artistic portrayals of psychedelic visionary experiences can be found in the field of visionary art (Grey, 1990; Luna and Amaringo, 1991; Masters and Houston, 1968; Mikosz, 2015) (Figure 1.13). Furthermore, psychedelic imagery resembles ancient visionary art as the one found in rock paintings and other artifacts (Lewis-Williams, 2002; Lewis-Williams, et al., 1988; Winkelman, 2002). Some indigenous tribes in Colombian Amazon decorate their homes with patterns and visions that are seen in ayahuasca ceremonies (Lagrou, 1998; Langdon, 1979; Reichel-Dolmatoff, 1972), and many western ayahuasca tourists (Kavenská and Simonová, 2015) return home with indigenous art such as the geometrical patterns found on textiles by Shipibo people (Figure 1.10). In Psytrance festivals and raves, video art next to the [stage](#) resemble psychedelic imagery and some festivals have a [museum](#) for visionary art. Besides attempting to portray the psychedelic experience, visionary art serves as a cultural tool that unifies groups around symbols which are derived from one’s own intimate mind yet shared by many minds: visionary art reveals how universal the personal is.

1.6.4 Simple vs Complex Imagery

Many differentiate between simple and complex imagery (elementary vs complex in Klüver (1928) ,non-figurative vs. figurative in Shanon (2002a); entoptic vs. eidetic in Kent (2010) as in Klüver (1926); *noméri* (luminous patterns), *toondari* (clusters), or *tere* (grids and zigzags) vs. unsymmetrical complex imagery in Amazonian Tokano

people (Reichel-Dolmatoff, 1975); temporal differentiation in Kometer and Vollenweider (2016); and the differentiation into elementary and complex imagery in Altered State of Consciousness (ASC) questionnaire (Dittrich, 1998; Studerus, et al., 2010)). In this section I briefly present the phenomenology of simple and complex psychedelic imagery.

The first modern analysis of the geometry of psychedelic imagery was conducted by Klüver when he administered peyote to himself and his subjects (Klüver, 1926). Klüver found few patterns that were reoccurring between subjects. These he named “form constants” which are Lattices, Cobwebs, Tunnels and Spirals (Klüver, 1928; Klüver, 1942) (Figure 1.11). Geometric patterns tend to be symmetrical, kaleidoscopic and with movement. Similar form constants, as those described by Klüver, have been found in other situations such as near-death experiences, hypnagogic states, Charles Bonnet Syndrome, ocular pressure, sensory deprivation, sensory overstimulation, flickering lights, transcranial magnetic stimulation (TMS) pulses, and extensive chanting or rhythmic drumming (Billock and Tsou, 2012; Siegel, 1977). Furthermore, it is suggested that these patterns are cross-cultural (Siegel and Jarvik, 1975), and relate to the topography of the visual cortex (more on this below, 1.9.2) (Bressloff, et al., 2002; Ermentrout and Cowan, 1979).

More detailed description of psychedelic simple imagery is described by Amazonian Tukano people in Colombia who categorized recurrent shapes of “*Gahpí ohori*” (yajé images) much earlier than Klüver (Figure 1.12) (Mikosz, 2015; Reichel-Dolmatoff, 1978). The Tukano describe approximately 20 shapes, and each one of them has its own local interpretation. These shapes are elegantly compared, with surprising resemblance, to phosphenes induced by cortical stimulation in more than 1000 subjects in experiments of Max Knoll (Oster, 1970; Reichel-Dolmatoff, 1975). The similarity between electrical stimulated phosphenes and Tukano’s drawing of simple imagery (Figure 1.12) strongly support the suggestion that simple imagery has an entoptic origin within the visual system.

Complex imagery might consist of autobiographical memories (Shanon, 2002b; Studerus, et al., 2011), or might be of different realities, cities and temples, and encounter with entities, deities, demons, or tricksters (Cott and Rock, 2008; Harner, 1973; Luke, 2011; Shanon, 2002a; Strassman, 2000). Complex imagery can be common across people and cultures (e.g jaguars and snakes with ayahuasca) (Harner, 1973; Reichel-Dolmatoff, 1975; Shanon, 2002a), or it can be very specific to one's own biography and culture (Langdon, 1979; Reichel-Dolmatoff, 1975; Shanon, 2002a). Sometimes, complex imagery can be utilized for creative problem solving³ (Harman, et al., 1966). Complex imagery is more stable than simple imagery, which is transient (Reichel-Dolmatoff, 1975). It is worth mentioning that in many situations one is fully immersed, with all of his/her senses and selfhood, into a different "reality" and is not just passively viewing imagery. Therefore, in shamanic traditions, complex imagery is considered to be a superior form of imagery as one "travels" to "other realms" (Reichel-Dolmatoff, 1975; Shanon, 2002a; Winkelman, 2010).

1.6.5 Dynamics of Experience

The experience of psychedelic imagery tend to progress from simple imagery at the onset to more complex imagery at peak (Klüver, 1928; Knauer and Maloney, 1913; Lewis-Williams, 2002; Reichel-Dolmatoff, 1975; Shanon, 2002b). Knauer and Maloney (1913) (from Klüver (1928)) described the mescaline sequence as: wavy lines; mosaics; carpets, floral designs, ornaments, wood-carving; wind-mills; monuments; mauseoleums; panoramic landscapes; statuesque men and animals; scenes with narrative.

Meyer described the DMT progression in 4 stages (Luke, 2011; Meyer, 1994): 1) Threshold experience; an interior flowing of energy/consciousness. 2) Vivid,

³one famous example of psychedelic creative problem solving is of Kary Mullis, the Nobel Prize winner, who claimed that LSD assisted him to vision the solution that led to the invention of polymerase chain reaction (PCR) (Kounen (2004)

brilliantly coloured, geometric visual patterns; geometries are basically two-dimensional but may pulse. *Transitional phase*: Tunnel or breakthrough experience; passage through an entrance into another world. 3) Three- or higher-dimensional space, possible contact with entities; a sense of being in an 'objective' space and of meeting intelligent and communicating entities. 4) The white light.

Reichel-Dolmatoff (1975), suggests, based on Tukano people, three sequential stages of the ayahuasca experience. The first include phosphenes, symmetrical, geometric and kaleidoscopic patterns. He suggest that this stage is neurologically determined without cultural variable (Figure 1.12). In the second stage the symmetry and geometry disappear and figurative imagery appears, which tend to be culture dependent (e.g different deities from Tokano's mythology or frightening beasts). This stage is interpreted by the Tukano people as the return to the maternal womb and a rebirth process (similar to Grof's Basic Perinatal Matrices that focus on rebirth as well (Grof, et al., 1980)). In the third stage, images disappear and a soft yellow light appears which is associated with a serene blissful state.

A more detailed progression of ayahuasca imagery is described by Shanon (2002a): 1) Bursts, puffs and splashes of color. 2) Repetitive, multiplying non-figurative elements. 3) Geometric designs and patterns (abstract). 4) Designs with figures. 5) Rapid figural transformations (e.g. similar to time-laps videos of an opening flower, moving clouds). 6) Kaleidoscopic images. 7) Well-defined, stable, single figurative images. 8) Proto-scenes (brief flashes of scenes). 9) Full-fledged scenes (passive, similar to watching a movie). 10) Interactive scenes. 11) Scenes of flight. 12) Celestial and heavenly scenes. 13) Virtual reality (when one is fully immersed into another reality with all of his senses). 14) Supreme light. Shanon (2002a) emphasis that progression in stages is not necessarily temporal and not all stages occur (stages 11 and 12 are actually not stages, but are in the list as they are common experiences of very meaningful scenes, stages 13 and 14 are very rare). He continues to suggest that some stages like geometrical patterns can occur later in the experience, but they tend to be in the transition to a

‘stronger’ visual experience – serving as the “fence” to another more complex “reality” (p.278).

Another description of progression by Shanon (2002a) is of ‘Visual strength’, which is depicted in 13 different lines of progression. 1) Progression towards the figurative; 2) towards well-definedness 3) towards stability; 4) towards globality; 5) towards contentual richness; 6) towards extended scope; 7) towards sensed reality – experienced as real; 8) towards psychological significance; 9) towards spiritual impact; 10) towards higher degrees of interaction – the user become more actively involved; 11) towards immersion; 12) towards higher degrees of narrative complexity; 13) towards enhanced ideation – as the experience is of given knowledge, a noetic quality (James, 1902).

Generally, all of the above phenomenological models discuss the transition from simple to complex imagery, and regard complex imagery as more informative. For a suggestion of the neural mechanisms that might be involved in the differentiation between simple and complex see section 1.9.8

“If you see only dibujos [geometric design] you are still very much behind”

— Yebamasa Shaman (Deltgen, 1979)

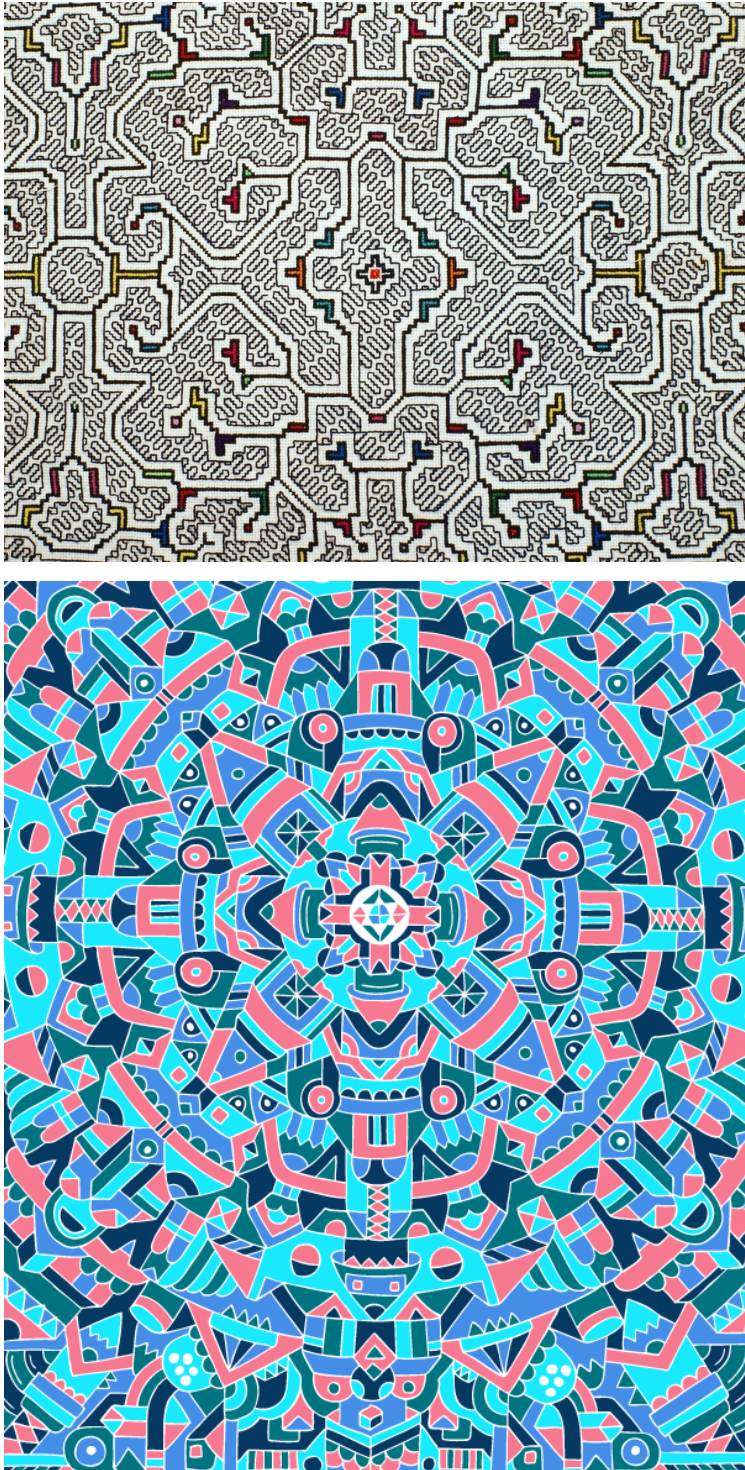


Figure 1.10. Visionary Art, Simple Imagery

Top: Shipibo textiles; *Bottom:* Switch by Sam Perkins, from effectindex.com

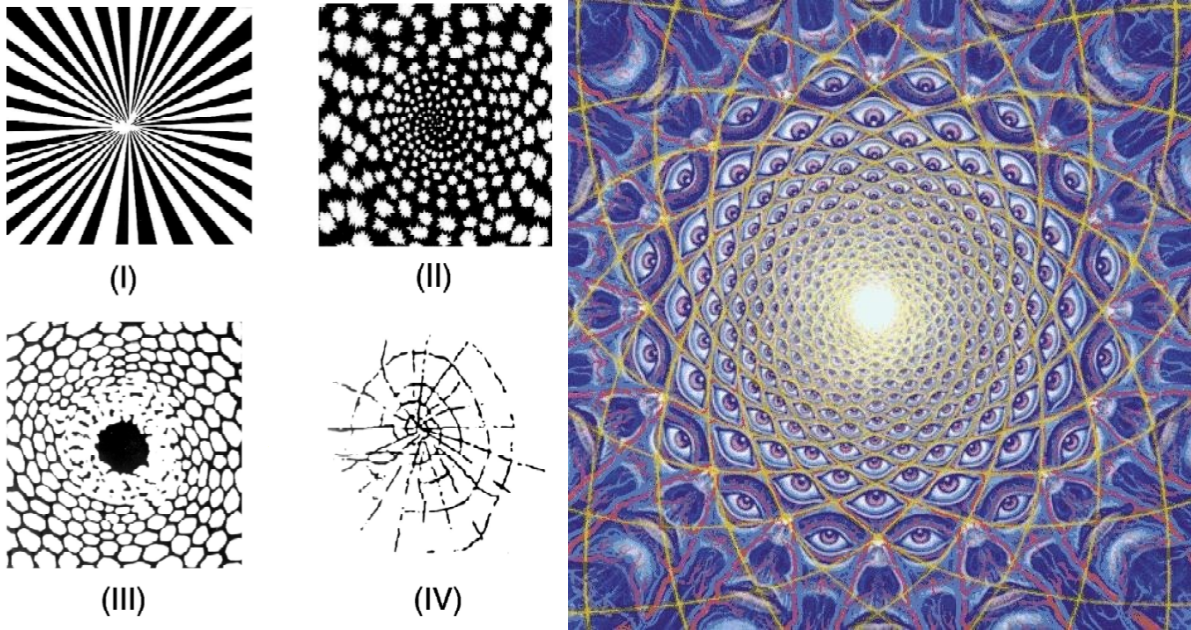


Figure 1.11. Simple Imagery – Klüver's Form Constants

Left: Klüver's mescaline form constants (Klüver, 1928; Klüver, 1942). I) Tunnels and Funnels; II) Spirals; III) Lattices (e.g Honeycombs and triangles); IV) Cobwebs. *Right:* Alex Grey's "Collective Vision" as an example of how complex imagery (eyes) can be constructed on top of simple imagery (Klüver's lattices), as in Shanon (2002a) description of kaleidoscopic vision.



Figure 1.12. Ayahuasca vs. Electric Stimulation Phosphenes

From Reichel-Dolmatoff (1975).

Top: Codified drawings of the Tukano people, represent different geometrical patterns that are perceived under the influence of ayahuasca in the first stage of the intoxication. These drawings are found also in house decorations, wall paintings, clothes, musical instruments, and more. Each drawing has meaning that is given locally by the Tukano (e.g 1 – Male; 2- Female; 3 – Fertilized Uterus; 4 – Entrance to uterus (marks the transition stage between different states of consciousness); 5 – Semen; 6 – Anaconda; 7 – “Our people” or “Other People” (depend on color of dot); 8 – reciprocal relationship between groups, etc.).

Bottom: Phosphenes perceived by more than 1000 subjects stimulated with low-voltage square-wave electric pulses by Max Knoll (Oster, 1970). Reichel-Dolmatoff compared Tukano and Knoll’s drawings the following way (Tukano-Knoll): 1-13; 2-9; 6-3; 7-9; 8,9-12; 10-10; 11-15; 13-7; 14-1; 15-2; 17-3; 18-4. This elegant comparison strengthen the hypothesis that simple imagery induced by psychedelics are culture

independent and therefore universal and entoptic – they emerge from within the visual system in the brain.



Figure 1.13. "Los Cachiboleros" by Pablo Amaringo (2002)

1.7 Mystical-Type Experience

Though not necessarily related to psychedelic imagery, I would like to shortly describe mystical-type experiences within the content of psychedelic use, as these relate to the emotional and “spiritual” component that motivates many, across cultures, to use classic psychedelics (Lee and Shlain, 1985; Pahnke and Richards, 1966; Winkelman, 2010). The so-called ‘mystical’ experience has been a classic problem area for mainstream psychology - if not science more generally. The term ‘mystical’ is particularly problematic, as it suggests associations with the supernatural that may be obstructive or even antithetical to scientific method and progress. It is important to note that by referring to mystical-type experience, I’m referring to the phenomenology of the experience and not to the interpretation of it. Readers interested in the phenomenology of mystical-type/peak experiences may wish to explore these classic texts (Csikszentmihalyi and Csikszentmihalyi, 1988; Hood Jr, et al., 1985; James, 1902; Maslow, 1964; Pahnke and Richards, 1966; Richards, 2015; Stace, 1960).

In the late 1960s, William Richards and Walter Pahnke (former pupils of Abraham Maslow and Timothy Leary, respectively) developed a measure of ‘peak’ or ‘mystical-type’ experience that was much inspired by the work of Walter Stace (Stace, 1960), and was designed specifically for psychedelic research. Studying reports of ‘mystical-type’ experiences occurring in a variety of different world religions, Stace identified a number of common or ‘universal’ components that are largely independent of religious or cultural context (Stace, 1960). The ‘universality’ of these components is grounded on perennial philosophy (Huxley, 1945) which assumes that many religions and spiritual traditions have a shared core unitive experience. Based on Stace’s landmark work, Richards and Pahnke developed the ‘mystical experience questionnaire’ (MEQ) designed to enquire whether related components featured in the psychedelic drug experience. The scale measured six components of experience: (1) sense of unity or oneness, (2) transcendence of time and space, (3) deeply felt

positive mood, (4) sense of awesomeness, reverence and wonder, (5) meaningfulness of psychological or philosophical insight, and (6) ineffability and paradoxicality (MacLean, et al., 2012; Pahnke and Richards, 1966; Pahnke, et al., 1970). These features are similar to Maslow's description of peak experience which can also occur in other conditions such as parental experience, childbirth (Balaskas, 1992; Gaskin, 1975), mystic/oceanic experience, aesthetic perception, creative moment, therapeutic or intellectual insight, orgasmic experience, and athletic fulfillment (Maslow, 1959). Evidence suggests that profound mystical-type experiences can be predictive of subsequent psychological health, whether induced by psychedelics (Bogenschutz, et al., 2015; Garcia-Romeu, et al., 2014; Griffiths, et al., 2016; Johnson, et al., 2016; Klavetter and Mogar, 1967; Kurland, et al., 1972; MacLean, et al., 2011; O'Reilly and Funk, 1964; Pahnke, et al., 1970; Richards, et al., 1977; Roseman, et al., 2017; Ross, et al., 2016), or other means (Belser, 2017; Csikszentmihalyi and Csikszentmihalyi, 1988; James, 1902; Ludwig, 1985; Maslow, 1959; Noyes Jr, 1980; Snell and Simmonds, 2015).

The experience of sensed unity is a central element of the mystical-type experience. Sensed unity can be internal or external (Pahnke and Richards, 1966; Stace, 1960). External unity is the experience in which the subject-object dichotomy, between self and outer world, dissolves. Internal unity is an experience in which all normal sense impressions cease and one experiences a selfless state, or ego-dissolution (Carhart-Harris, et al., 2014; Millière, 2017; Nour, et al., 2016), while a minimal experience of "pure consciousness" in an "ultimate reality" maintains. The unitive experience can have visionary component which resonates with descriptions of intense psychedelic imagery in which all that is experienced is white light (Meyer, 1994; Shanon, 2002a), as if the visual system is over stimulated (Fischer, 1971), or entirely entropic (Carhart-Harris, et al., 2014; Carhart-Harris, 2018), and one is experiencing an *ecstatic sensory overload*.

1.8 Neurophysiological Effects in Visual Cortex

1.8.1 Evoked activity

Many psychedelics studies of the visual system have been conducted by *stimulating* the visual system and measuring the excitability of different visual regions (retina, LGN and visual cortex). These studies could be generally separated into those which observed increased activity (Hyperexcitability) and those which observed decreased activity (Hypoexcitability).

Studies of the retina with Electroretinogram (ERG) under the influence of psychedelics have found increased retinal photic stimulation in cats (Apter and Pfeiffer, 1956) and increased tonic activity of the retina in cats (Schwartz and Cheney, 1965). Though, a different study showed that retinal increases in activity occurs only in very high doses and not in lower doses (Jacobson and Gestring, 1959). Furthermore, the same study showed that a section of the optic tract blocks this effect, suggesting that the retinal activity is due to decrease of inhibitory feedback from the optical tract. Increased retinal activity in humans have been observed (Krill, et al., 1960; Rodin and Luby, 1966) – yet the same researchers reported that visual hallucinations can occur in blind subjects without a functioning retina (non-congenital blind) (Krill, et al., 1963), suggesting the retina is not necessary for visual imagery.

Studies of the LGN show mixed results. One study showed increased tonic activity in LGN in cats (Schwartz and Cheney, 1965). While other studies showed hypoexcitability of optical tract and LGN to photic stimulation and optic nerve stimulation in cats (Evarts, et al., 1955; Phillis, et al., 1967), and photic stimulation in baboons (Meldrum and Naquet, 1971). Furthermore, decreased LGN postsynaptic transmission has been observed but no changes in presynaptic LGN, in cats (Bishop, et al., 1958; Bishop, et al., 1959) and in baboons (Walter, et al., 1971).

Studies of visual cortex showed mixed results as well. Hyperexcitability was observed in visual cortex to shock applied to optic radiation in cats (Evarts, et al., 1955) and to photic stimulation in cats (Da Fonseca, et al., 1965), rabbits (Steiner and Sulman, 1963) and in humans (Gastaut, et al., 1953; Kometer, et al., 2011). Furthermore, LSD increased the intensity and complexity of the phosphenes induced by electric stimulation in humans (Knoll, et al., 1963) and by stroboscopic light (Smythies, 1960), suggesting increased cortical excitability. But, hypoexcitability of visual cortex to electric stimulation has been observed in cats (Marrazzi, 1957), to LGN stimulation in rabbits (Yanagisawa, 1960), to optic chiasm stimulation in cats (Moore, et al., 1976; Moore and Domino, 1978), and to photic stimulation in rabbits (Khazan and McCash, 1965; Yanagisawa, 1960), baboons (Meldrum and Naquet, 1971), and humans (Rodin and Luby, 1966).

Some behavioral studies suggest increased visual excitability. Increased duration of after image in humans was found (Hollister and Hartman, 1962) and so does increased colors perceived in after-image, flicker and audio tones (Hartman and Hollister, 1963). Furthermore, an after image can suppress a perception of a new stimulus. After image suppression of perception is an objective measure of after image intensity. Increased after image suppression was observed in humans with psilocybin, and this suppression correlated with the subjective ratings of visual hallucinations (Keeler, 1965).

1.8.2 Evoked Activity - Dose Dependent

The discrepancy between confusing results of different labs regarding hyper- or hypo-stimulation was already noted by Harry Grundfest in 1956 at a conversation mentioned in Purpura (1956): *"I would like to stress two other aspects. These concern the old bugaboos of neurological research work and involve the effects of anesthesia. Both groups of experimenters have demonstrated that different kinds of anesthesia have different and recognizable effects which are revealed by the action of LSD. The*

second bugaboo is the differential effect of drug concentration. The difference in response to different concentration of drugs can be quite remarkable if one asks questions of the organism properly".

Since the above criticism (1956), some studies have addressed questions of drug concentration. These studies observed increased visual excitation in low doses, and decreased excitation in high doses in cats (Dray, et al., 1980; Foote, 1982; Fox and Dray, 1979; McKay and Horn, 1971; Purpura, 1956; Rose and Horn, 1977). Furthermore, optic chiasm stimulation in cats had reduced cortical response in high doses of LSD and DMT but not in low doses (Moore, et al., 1976; Moore and Domino, 1978). In many of animal studies very high doses are used, compared to human studies. Therefore, it is suggested that the effect of psychedelics in average doses taken by humans will lead to hyperexcitability, yet hypoexcitability might be observed in very high doses, or in peak drug effects. A pharmacological explanation to this dose dependency is strengthened by observation showing that 5-HT_{2A} mRNA expression on both glutamatergic (excitatory) and GABAergic (inhibitory) neurons, with lower binding on GABAergic (in PFC and other cortical regions) (Araneda and Andrade, 1991; De Almeida and Mengod, 2007; Halberstadt, 2015; Jakab and Goldman-Rakic, 2000; Mengod, et al., 2015; Santana, et al., 2004; Tanaka and North, 1993; Willins, et al., 1997). Therefore, high doses or peak drug effects might be accompanied with stronger inhibitory processes. This dose dependency aspect is also observed phenomenologically: at low to regular doses, different visual features intensify (e.g brightness, saturation and contrast) (Díaz, 2010; Dittrich, 1998; Fischer, et al., 1969; Klüver, 1928; Klüver, 1942; Rümmele and Gnirss, 1961), while in high doses external perception could be overridden by internal imagery (Cott and Rock, 2008; Shanon, 2002a; Strassman, 2000), and with very high doses, one can experience an all-encompassing white light or a blackout (Meyer, 1994; Shanon, 2002a). Furthermore Winkelman (2010) and Fischer (1971) suggest that the psychedelic experience has an ergotropic state (sympathetic system, similar to hyperexcitability),

which can intensify and “collapse” to trophotropic trance state (parasympathetic system, similar to hypoexcitability) (see section 1.9.6).

1.8.3 Spontaneous Activity

The above studies discuss activity of the visual cortex in response to stimulation. Other studies addressed changes in spontaneous activity. Decreased spontaneous cortical activity in visual cortex was observed in cats (Evarts, et al., 1955). But, also increased spontaneous retinal and LGN activity was observed in cats (Apter and Pfeiffer, 1956; Mouriz-Garcia, et al., 1969). Furthermore, increased PGO spikes was observed in LGN of cats in waking and slow wave sleep but not in REM (Morgane and Stern, 1972), suggesting similarity between the psychedelic state and dream state (Carhart-Harris, 2007). Again, this discrepancy might be dose related as decreased spontaneous firing rate in LGN was observed in cats, with high doses, but some increases with low doses (McKay and Horn, 1971). I would like to emphasize that the separation between spontaneous and evoked is not clear cut, as spontaneous activity which originate in the cortex becomes evoked activity in regions which receive the information from its original spontaneous origin (low level subthreshold activity which is usually not affecting other regions, might become intensified through hyperexcitability).

No clear conclusions can be made from the above studies regarding hyperexcitability or hypoexcitability, yet it is assumed that 5-HT_{2A} activation has a general depolarizing effect (Andrade, 2011; Araneda and Andrade, 1991; Celada, et al., 2013; Nichols, 2016), and that psychedelics increase excitatory postsynaptic currents (EPSCs) of pyramidal neurons, especially in layer 5 of the cortex (Aghajanian and Marek, 1997; Béïque, et al., 2007; González-Maeso, et al., 2007; Muthukumaraswamy, et al., 2013; Riga, et al., 2014), and shift the excitatory-inhibitory balance in occipital cortex – in favour of excitability (William Moreau, et al., 2009). Yet, it is possible that exciting inhibitory neurons can lead to inhibition (Andrade, 2011).

To add a level of complexity, 5-HT_{2A} agonists exerted bidirectional modulatory effects on the firing rate of neurons in V1: neurons with low firing rate in baseline were accentuated and neurons with high firing rate in baseline were suppressed (Watakabe, et al., 2008). This is quite intriguing, as psychedelics can flip V1 activity from processing external stimuli to processing internal “background” activity (Kometer and Vollenweider, 2016; Watakabe, et al., 2008). Indeed, subjectively, with large doses, psychedelic imagery can completely “cover” or mask eyes open vision of the external environment (Shanon, 2002a).

Few modern human fMRI psychedelics studies support the notion that the visual cortex is involved in psychedelic imagery. Elevated fMRI BOLD activation (reduced deactivation) in the visual cortex during the induction of eyes-closed visual-imagery has been seen in studies with ayahuasca (de Araujo, et al., 2012) and psilocybin (Carhart-Harris, et al., 2012c) and correlation was found between psychedelic imagery and metabolic rates in occipital cortex, striatum, temporal cortex and frontal-parietal network (Vollenweider and Geyer, 2001). Increased communication with other brain regions has been observed as well and recently our group detected significant increases in resting-state functional connectivity (RSFC) between visual networks and higher-level associative networks with psilocybin (Roseman, et al., 2014). Moreover, functional connectivity between thalamus and fusiform gyrus correlated with psychedelic imagery, under LSD (Mueller, et al., 2017). Increased functional connectivity between parahippocampus and visual cortex was observed for the interaction of music and LSD - suggesting that music together with LSD may have facilitated the emergence of memories and imagery from parahippocampus (Kaelen, et al., 2016), supporting the influence of context (music) on the experience (Carhart-Harris, et al., 2017; Hartogsohn, 2017; Studerus, et al., 2012). These studies suggest that both the activity of the visual cortex and the communication between visual cortex and other regions are crucial for the emergence of psychedelic imagery.

1.8.4 Alpha Suppression

Alpha frequency (8-12 Hz) is the dominant frequency in the human cortex and is strongest in occipital-parietal cortex (Bas, et al., 1997). Suppressed occipital alpha is a brain hallmark of moving from eyes closed to eyes open, and thalamocortical relay cells show alpha activity in a state of decreased sensory information (Llinás, 1988; Steriade, 2000). Hence, it is suggested that alpha is related to the gating mechanism in the thalamus (da Silva, 1991) and that alpha serve an inhibitory function across the visual cortex (Foxe and Snyder, 2011; Haegens, et al., 2011; Klimesch, 1999; Klimesch, 2012; Thut, et al., 2006). Decreased alpha power is associated with increased neural firing (Haegens, et al., 2011), increased BOLD signal in visual cortex (Goldman, et al., 2002), decreased perceptual threshold (Ergenoglu, et al., 2004; Thut, et al., 2006; Van Dijk, et al., 2008), and increased phosphenes induced with TMS (Romei, et al., 2008; Romei, et al., 2010). It can be inferred, that decreased alpha power relates to increased activity and thus excitability, as alpha is related to inhibitory top-down processes (Halgren, et al., 2017; Van Kerkoerle, et al., 2014).

Flattening of the EEG and particularly reduction in alpha power frequency in the occipital cortex is the most replicated result in psychedelic research, both in animal studies (Bradley and Elkes, 1953b; Bradley and Elkes, 1957; Elkes, et al., 1954; Fairchild, et al., 1980; Himwich, 1956; Horovitz, et al., 1965; Ingvar and Söderberg, 1956; Kanako, et al., 1960; Langfitt and Finney, 1959; Monnier, 1957; Steiner and Sulman, 1963; Takagi, et al., 1958), and in humans with psilocybin (Kometer, et al., 2013; Muthukumaraswamy, et al., 2013; Thatcher, et al., 1971), ayahuasca (Alonso, et al., 2015; Riba, et al., 2004; Schenberg, et al., 2015), LSD (Carhart-Harris, et al., 2016a; Fink, 1959; Monroe, et al., 1957a; Pfeiffer, et al., 1965; Rodin and Luby, 1966; Schwarz, et al., 1956), mescaline (Monroe, et al., 1957a; Schwarz, et al., 1956), DMT and 5-MeO-DMT (Acosta-Urquidi, 2015; Timmermann, et al., 2018). The relationship between decreased alpha power and psychedelic imagery was found to be related to 5-HT_{2A}R activation as this effect was blocked with a 5-HT_{2A}R antagonist (Valle, et al., 2016). Relationship between decreased alpha power and DMT plasma

levels was observed with ayahuasca (Schenberg, et al., 2015). Furthermore, alpha power reduction relates to the intensity and complexity of visual imagery *within* subjects as well as in between subjects with LSD (Shirahashi, 1960) and it correlates with the subjective intensity dynamics of DMT *within* subjects (Timmermann, et al., 2018). It is important to note, however, that some studies show some increased synchronized response in low frequencies – with a very high dose of LSD compared to lower doses in cats (Horovitz, et al., 1965); in quiet environment compared to noisy environment in cats (Bradley and Key, 1958); and with DMT and 5-MeO-DMT in humans (Acosta-Urquidi, 2015; Timmermann, et al., 2018). More on increased theta power in 1.9.5.

The notion that alpha suppression, induced by psychedelics, relates to decreased inhibitory function, and increased excitability, is supported by a few studies: 1) Reduced rhythmic after discharge of visually evoked occipital potential disappears as spontaneous EEG signal becomes progressively suppressed (Rodin and Luby, 1966). 2) Psychedelics increased sensitivity to phosphenes induced with electric stimulation (Knoll, et al., 1963; Romei, et al., 2008; Romei, et al., 2010) and stroboscopic light (Smythies, 1960). 3) Pre-stimulus alpha suppression correlated with post-stimulus increase in P1 potential in the visual cortex (Kometer, et al., 2013). Though, none of these studies can conclude that the alpha suppression leads to increased excitation, or that increased excitation leads to alpha suppression.

Before speculating on the mechanism in which alpha suppression relates to psychedelic imagery, it is important to note other conditions in which alpha power decreases. These are: visual stimulus with eyes open (Hanslmayr, et al., 2007; Klimesch, 2011) or closed (Pfurtscheller and Aranibar, 1977), increased attention (Foxe, et al., 1998; Kelly, et al., 2006; Worden, et al., 2000), increased anticipatory attention (Bastiaansen and Brunia, 2001), mental imagery (Salenius, et al., 1995; Schupp, et al., 1994; Slatter, 1960), increased attention to details of mental imagery (Salenius, et al., 1995), phasic-REM (with eye movements) compared to tonic-REM

(without eye movements) (Cantero, et al., 1999), and with stimulants such as amphetamine, cocaine and caffeine (Deslandes, et al., 2005; Fink, 1969; Monnier, 1957; Pfeiffer, et al., 1965; Siepmann and Kirch, 2002).

As alpha suppression occurs in other visual or aroused conditions - whether by stimuli, imagination, dreams, stimulants and psychedelics - it is important to be cautious regarding the interpretation of alpha suppression. One might interpret that psychedelics lead to alpha suppression which “amplif[ies] internal-driven excitation” and therefore give rise to psychedelic imagery (Kometer and Vollenweider, 2016). Yet, correlation does not imply causation, and it is possible (and simpler) to interpret the alpha suppression as a state that occurs in the processing of psychedelic imagery as it occurs in the processing of other imagery or visual stimuli, and might even be the effect of the imagery and not necessarily the cause. Nonetheless, alpha suppression is the most reliable correlate of the psychedelic state, and it can serve as a marker for the visual intensity of the psychedelic experience.

1.9 Mechanistic Models of Psychedelic Imagery

Though many models and theories exist that attempt to describe the psychedelic mind at large, I will focus in this section on theories which are more specific for psychedelic imagery. In some cases the theory which will be mentioned is relevant for the general effect of psychedelics, and in cases like this I will focus on sections within this theory that are more relevant to psychedelic imagery. Some of the theories may overlap, and they are not necessarily exclusive to the authors that present them.

1.9.1 Visual Hierarchy

The progression of psychedelic imagery is very possibly related to an increasing involvement of different regions in the visual hierarchy (Figure 1.1) – from low level

visual areas to higher level visual areas. This is supported by non-psychedelic stimulation studies that show that stimulation of different areas in the visual cortex induce hallucinations based on the location of the stimulation in hierarchical manner: simple hallucinations in low level visual areas and complex in high level visual areas (Lee, et al., 2000). Intensity and complexity of visual imagery is dose dependent (Studerus, et al., 2011) and as primary visual cortex (V1) has more expression of 5-HT_{2A}R than other higher visual areas (Beliveau, et al., 2017; Watakabe, et al., 2008; Zilles, et al., 2002) (Figure 1.8), one can assume that it is more sensitive to 5-HT_{2A}R agonists than other visual areas, and therefore low doses of psychedelics will generate geometrical imagery in V1 and not complex imagery in higher areas, and with high doses the experience will progress from simple to complex imagery as effects will start with V1 which has more receptors.

1.9.2 V1 topography (Ermentrout and Cowan, 1979)

A few mathematical models show how increased excitation can generate geometric hallucinations according to the topographic architecture of the visual cortex (Figure 1.2 and 1.3 for retinotopic organization of visual cortex). Elegantly, these models predict Kluver's (1928, 1942) forms constants (Figure 1.11) which are consistent geometrical imagery across subjects (Billock and Tsou, 2012; Bressloff, et al., 2001; Bressloff, et al., 2002; Butler, et al., 2012; Ermentrout and Cowan, 1979; Gutkin, et al., 2003; Rule, et al., 2011). Furthermore, geometrical imagery is considered culture-independent and therefore it probably relates to low level visual processing (Reichel-Dolmatoff, 1975; Siegel and Jarvik, 1975). Ermentrout and Cowan (1979) proposed a mechanism by which Kluver's patterns could be perceived that is based on aberrant waves of excitation spreading across the approximately log-polar retinotopic map of primary visual cortex (waves are transformed from *cortex to perception* in an inverse transformation of the "*stimuli to cortex*" retinotopic transformation) (Figure 1.14). Their model (and it's future developments (Bressloff, et al., 2001; Bressloff, et al., 2002; Butler, et al., 2012) involve two elements. The first is asymmetry between excitation and inhibition processes (more excitation), and the second is a diffusion

mechanism that spreads the activity. This results in waves of spontaneous activity that spread through lateral interaction. The spread of activity is transformed into visual perception which is experienced in retinotopic fashion (Ermentrout and Cowan, 1979) and in relation to V1 organization as hypercolumns (of Orientation Tuning) (Blasdel, 1992; Bressloff, et al., 2001; Hubel and Wiesel, 1974).

These mathematical models are based on Turing mechanism that originally explained morphogenesis using a reaction-diffusion model of two interacting chemicals: activator (e.g. pigment) and inhibitor. The inhibitor and activator diffuse in different rates in a state of instability. When the inhibitor diffuses faster than the activator it forces the activator to stay in stripes or patches (Turing, 1952) (Zebras and Tigers being the classic examples of Turing's morphogenesis). When transforming Turing's model from chemicals into neural tissue - instead of calculating diffusion constants of two chemicals - space constant of excitation and inhibition is calculated (Wilson and Cowan, 1972). Turing's mechanism in neural tissue can create stripes and patches as well, and they are experienced as Kluver's form constants when transformed from cortex to perception (Figure 1.14).

The propagation of spontaneous waves is dependent on lateral inhibition (Ermentrout and Cowan, 1979): excitatory neurons are connected to neighboring neurons with lateral inhibition. When these neurons are excited they inhibit their neighbors, but when the neighbors are inhibited they do not inhibit their own neighbors and therefore, the neighbors of neighbors are excited as well. In this way different stripes are created on the cortex based on lateral inhibition connections. When critical point of local equilibrium state becomes unstable this leads to spontaneous symmetry breaking and patterns and waves immerge.

Another example of how psychedelic geometrical imagery is dependent on visual cortex topography is related to the size of receptive fields: cortical regions which process peripheral vision have larger receptive fields than foveal regions (center of

vision has higher resolution and therefore requires larger cortical areas) (Serenio, et al., 1995). Therefore, geometrical patterns in the periphery seem larger than the patterns in foveal areas, as the receptive fields in the periphery are larger. This element of psychedelic imagery is described nicely in some visionary art and in Kluver's form constants (Figures 1.11).

While models which are based on V1 topography are good in explaining geometric imagery they cannot explain complex imagery. Though, it is important to note that sometimes complex-imagery is presented in a highly geometric fashion. That is to say that lower level visual areas might still be active in the processing of complex imagery. Moreover, in case simple geometric patterns play part in complex imagery, it can explain why animals such as snakes and tigers are common in imagery (Shanon, 2002a), as their geometrical patterns are based on similar Turing morphogenesis mechanism as simple imagery.

1.9.3 Inhibition of Thalamic Sensory Gating (Vollenweider and Geyer, 2001)

Vollenweider and Geyer suggest that functional disturbances within cortico-striato-thalamic-cortical (CSTC) feedback loops lead to the psychedelic experience including psychedelic imagery. They suggest that thalamic gating is disrupted and therefore both internal and external information/stimuli is intensified, a condition which could lead to information/stimulus overload that can disrupt higher level functions as well. The model is based upon five segregated CSTC loops functioning in parallel: motor, oculomotor, prefrontal, association and limbic loops. The reduction of the thalamic filter in this model echoes the "*reducing valve*" theory suggested by Huxley (1954).

1.9.4 Increased low-level and decreased high-level processing (Kometer and Vollenweider, 2016)

It is suggested that psychedelics work by both increasing low-level visual processing (e.g brightness, contrast and saturation) and impairing high-level visual processing (e.g perception of whole objects, detection of global motion patterns, construction of visual space) (Kometer, et al., 2011; Kometer, et al., 2013; Kometer and Vollenweider, 2016). The low level visual features are processed fast compared to the high level visual features that are processed slower up the hierarchy. Kometer showed increased low-level event-related P1 amplitude, and decreased mid-level event-related N170 amplitude (Kometer, et al., 2013). N170 is related to object completion and is usually high in response to Kanisza figures (an incomplete triangle that is perceived as complete by mid-level visual integration which N170 is associated with). The difference in N170 between psilocybin and placebo was related to the subjective ratings of psychedelic imagery (Kometer, et al., 2011). The increase in P1 and decreases in N170 suggest that the visual system become more excited though less integrated.

1.9.5 Temporal Lobe Theta Bursts (Carhart-Harris, 2007)

Carhart-Harris argues for the involvement of the temporal lobe in psychedelic imagery. This is also argued by others (Kent, 2010; Winkelman, 2010), but it is summarized thoroughly in Carhart-Harris (2007). Furthermore, this is the first, and relatively unknown paper of Carhart-Harris (who supervised this thesis), and I am enjoying discussing it here. Carhart-Harris argues for a similarity between four different imagery states: the dream state, the dreamy state of temporal lobe epilepsy and stimulation, the acute psychotic state, and the psychedelic state. All of these states are related to increased theta bursts and slow wave activity (2-8Hz): “An argument is made that bursts of electrical activity spreading from the medial temporal lobes to the association cortices are the primary functional correlate of discharging psychical energies, experienced on a subjective level as the emergence of unconscious material into consciousness”. Increased hippocampal theta bursts are related to experience of transcendence (Mandell, 1980), and some psychedelic studies

showed increased theta power in humans with EEG (Acosta-Urquidi, 2015; Timmermann, et al., 2018), and with depth recording in temporal lobe (Monroe, et al., 1957b; Schwarz, et al., 1956). Increased theta power was observed with LSD (Winters and Wallach, 1970) and was associated with the intensity of subjective experience (Monroe, et al., 1957b). Furthermore, under DMT, it was limited to peak drug effects (Timmermann, et al., 2018). Hippocampal and parahippocampal activation and connectivity were modulated under the influence of psychedelics and relate to the experience of ego-dissolution (Carhart-Harris, 2007; Carhart-Harris, et al., 2014; Carhart-Harris, et al., 2016b). Most importantly, temporal lobe lobotomy reduced psychedelic imagery in human epileptic⁴ patients (Serafetinides, 1965) and reduced LSD effects in chimpanzees (Baldwin, et al., 1959).

1.9.6 Ergotropic vs. Trophotropic (Winkelman, 2010)

Winkelman expands on a suggestion by Davidson (1976) and Fischer (1971): a common mechanism of altered state of consciousness is related to the ergotropic activation of the sympathetic system (hyperexcitability) which in intense experiences leads to a collapse into a trophotropic state (hypoexcitability). Winkelman suggest that many shamanic traditions use other techniques in which intense excitation lead eventually to a trophotropic state (e.g movement, pain) – a phenomenon called “rebound to superactivity” (Fischer, 1971). It is suggested that an intense immersion

⁴Dostoevsky whom had temporal lobe epilepsy, described the moments before full blown seizures as extremely blissful and ecstatic: “*A happiness unthinkable in the normal state and unimaginable for anyone who hasn’t experienced it... I am then in perfect harmony with myself and the entire universe*”. His experiences with temporal lobe epilepsy are represented in the protagonist of the “Idiot”, Prince Lev Nikolayevich Myshkin, which has a similar condition - a very good example of how art informed science.

into psychedelic imagery is a trophotropic trance state which is closer to mystical-type experience. The differentiation between ergotropic and trophotropic state resonates with the suggestion by Kent (2010) (below), in which increased excitability might lead to a re-synchronized state beyond destabilization. Winkelman suggest that the highly aroused ergotropic state is related to the observed reductions in alpha power, but that the re-synchronized trophotropic state is related to increased theta power. More on temporal activity in the section above (1.9.5).

1.9.7 Nonlinear Hallucinations (Kent, 2008; Kent, 2010).

5-HT_{2A}R agonists are found in high density in layer V that mediate cortical and thalamocortical feedback excitation in perceptual analysis. Therefore, 5-HT_{2A} receptor agonists can interrupt and/or amplify feedback processing. Kent emphasises that *"we must not ignore the possibility that 5-HT_{2A} receptor selective agonists may have multiple actions at multiple sites, serving to both dampen localized lateral inhibition while simultaneously promoting feedback excitation across the entire cortex. This dualistic effect would become synergistic at higher doses, serving to boost overall brain excitation by flooding disinhibited networks with uninhibited or runaway feedback processing loops"* (Kent, 2008).

Kent argues that because of the destabilization of the network, the visual cortex acts in a nonlinear way. In a nonlinear system the output feeds back on itself and becomes chaotic and complex – any small change can diverge exponentially and the output of the system cannot be easily predicted. Kent indicates that *"psychedelics are famous for being progressively nonlinear, which means incoming sensation saturates perception and begins to stack over itself, generating increasing complexity of sensual intensity through time"* (p.88, see Figure 1.15 for an example of a video feedback loop). A compelling phenomenon that supports Kent's argument is that under the influence of psychedelics, with eyes open, when one is focusing on an object, the

imagery will evolve in time, and will become stronger as long as the focus is held. When that person will look somewhere else he will “restart” the imagery. Some of the psychedelic imagery can begin in an entoptic fashion, based on spontaneous excitation in the visual system - between the retina and visual cortex - and this imagery will evolve all over the visual cortex in a nonlinear fashion.

Kent suggest that entoptic imagery (simple imagery) is mainly due to excitation and destabilization in corticocortical and thalamocortical feedback loops. However, increased excitability in high doses can reach a point beyond destabilization in which neurons will re-synchronize and these states can lead to peak experience or fully immersed visionary states (see also 1.9.6).

1.9.8 Parvocellular vs. Magnocellular Pathways

I would like to suggest an hypothesis regarding the difference between simple and complex imagery (non-figurative vs figurative in Shanon (2002a), entoptic vs eidetic in Kent (2010) as in Klüver (1926)). Simple vs. complex imagery might differentiate in the magnocellular and parvocellular pathways (Figure 1.4) that are involved in processing/generating the imagery. The magnocellular pathway (“where” pathway) begins mostly in the rods (peripheral retina) and ends in parietal cortex. It is peripheral, transient, and processing movement, location, and spatial relations. The parvocellular pathway (“what” pathway) begins mostly in the cones (foveal retina) and ends in temporal cortex. It is foveal, static, and is processing the content of vision. This hypothesis expands on the notion that the difference between simple to complex imagery is related to moving up the visual hierarchy, and adds another element which is related to organization of the visual cortex into two very distinct systems (Schneider, 1969).

Geometrical imagery is fast and most of the time does not involve any content. It is mainly related to spatial relations and movement. Furthermore, geometrical imagery is frequently described as tunnel vision (Figure 1.11), which means that it does not include foveal regions. In the purest sense, the features of simple imagery are in agreement with the magnocellular pathway.

Complex imagery is more static and with content, which is more in accordance with the parvocellular pathway. Furthermore, as mentioned above (1.9.5) it is suggested that the temporal lobe plays a crucial rule in the processing of complex imagery, as seen with EEG theta activity (Acosta-Urquidi, 2015; Timmermann, et al., 2018), and with depth recording in temporal lobe (Monroe, et al., 1957b; Schwarz, et al., 1956). Furthermore, temporal lobe lobotomy decreased intensity of psychedelic imagery in humans (Serafetinides, 1965). Stronger imagery is experienced in dimmed environment (Siegel and Jarvik, 1975), and indigenous shamans prefer night time to induce stronger imagery (Reichel-Dolmatoff, 1975). In darkness, retinal cones are less active, which means, based on this hypothesis, that psychedelic imagery has less of competition with regular vision in the parvocellular pathway, and therefore it is easier to perceive psychedelic complex imagery at night.

In other non-drug hallucinatory states such as in Charles Bonnet Syndrom, the hallucination was found to be related to specialized subregions in the ventral stream in accordance to the content of the hallucination (Howard, et al., 1998). Furthermore, visual hallucinations in Parkinson Disease Dementia (PDD) are associated with increased 5-HT_{2A} receptor binding in the parvocellular pathway (Ballanger, et al., 2010; Huot, et al., 2010), and 5-HT_{2A} inverse agonists can reduce visual hallucinations in PDD (Cummings, et al., 2014; Meltzer, et al., 2010).

DMT is a fast acting psychedelic and in a very short time one can experience many stages of the psychedelic experience. Therefore, transitions from geometric to complex imagery are abrupt. This transition is called a “breakthrough” experience as

one feels like he/she is “transported” to a different reality (Meyer, 1994). The breakthrough moment is a quick qualitative shift in experience and is not merely a quantitative intensification of the experience. I would like to speculate that this qualitative shift fits a transition from mainly magnocellular processing to parvocellular processing. Furthermore, many describe the first geometrical phase as moving in a tunnel and then reaching to “another reality”. The tunnel is mainly a geometrical peripheral experience with movement (magnocellular), and reaching the center of the tunnel (foveal) is associated with reaching a place with content (parvocellular). Therefore, I would like to suggest that one should consider not just the hierarchy of the visual cortex but also its separation to two different pathways.

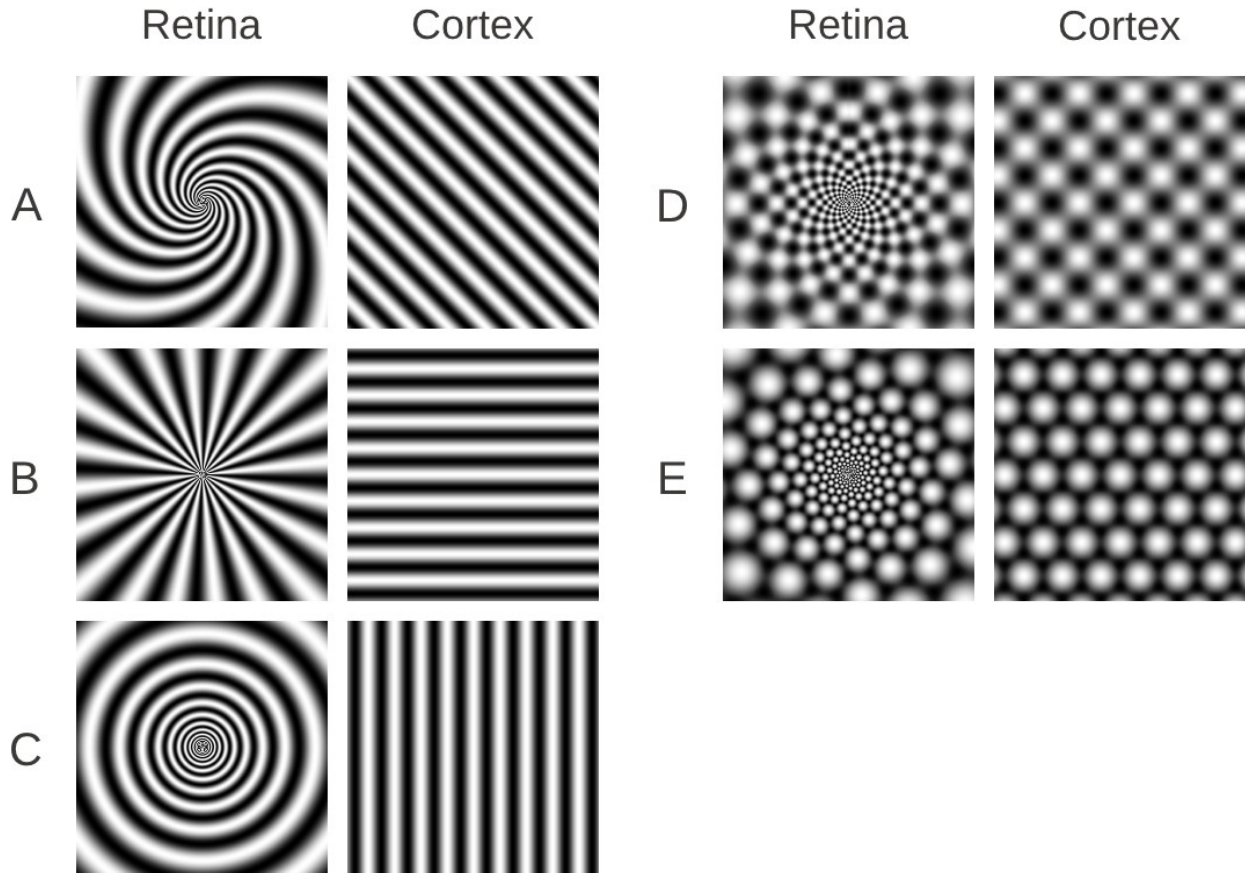


Figure 1.14. Inverse Retinotopic Transformation

From Rule, et al. (2011), reproduced without need for permission. Illustrations of basic phosphene patterns and their transformation to “cortical coordinates.” On the right are patterns of spontaneous activity in the cortex and on the left is the transformation to perception based on topography of the visual cortex. Notice how this relates to retinotopic mapping in Figures 1.2 and 1.3.



Figure 1.15. Video Feedback Loop

From Hofstadter (2007). Mentioned in Kent (2010). A video feedback loop occurs when a camera is pointed towards its own monitor. Kent use it as an example of nonlinear system: *"A video feedback loop creates a nonlinear system isomorphic of a fractal, which recedes inward on itself, spiraling towards infinite complexity under a second"* and *"A video feedback loop is a good example of a nonlinear perceptual system; each frame captures itself and the receding previous frame, and then itself and two receding frames, and then itself and three receding frames, and then itself and four receding frames, and so on, feeding back on itself at 30 frames per second until complexity recedes into chaos and infinity"* (p.77)

1.10 Objectives and Hypotheses

The main objective of this thesis was to test the involvement of the visual cortex in the processing of psychedelic imagery. Studies presented in this chapter have already suggested that the visual cortex is activated while processing psychedelic imagery. Therefore, the aim of the thesis was to expand on this notion by investigating other elements of visual cortex activity that are beyond activation, such as connectivity and dynamics.

Chapter 3 | Study 1 | V1 RSFC

Objective: to investigate patterns of communication between V1 and the rest of the brain. *Hypothesis:* under LSD, increased V1 connectivity patterns will be observed with other cortical and subcortical regions, and this will correlate with subjective ratings of psychedelic imagery and alpha power suppression.

Chapter 4 | Study 2 | Retinotopic Coordination

Objective: to investigate patterns of communication within visual cortex, based on retinotopic architecture. *Hypothesis:* under LSD, connectivity between subregions within the visual cortex (V1 and V3) will be according to their retinotopic architecture, and this will correlate with subjective ratings and alpha power suppression.

Chapter 5 | Study 3 | Dynamics

Objective: to investigate dynamics of activity within the visual cortex based on visual cortex hierarchy, and based on magnocellular and parvocellular streams. *Hypothesis:* during the onset phase of psilocybin, activity of visual cortex subregions will increase gradually “upstream” based on visual cortex hierarchy (low level to high level) and from magnocellular to parvocellular streams.

2. METHODOLOGY

“A scientist in his laboratory is not a mere technician: he is also a child confronting natural phenomena that impress him as though they were fairy tales.”

— Marie Curie

2.1 Introduction MRI and fMRI

2.1.1 How Does MRI Work?

Magnetic resonance imaging (MRI) is a method that utilizes strong magnetic fields with the combination of radio frequency (RF) energy to measure different elements of the tissue which relate to properties of hydrogen protons of water (Lauterbur, 1973; Mansfield and Grannell, 1973; Plewes and Kucharczyk, 2012). The MRI bore is the area within the MRI scanner in which the subject is lying and where the magnetic field is concentrated. The head coil has RF transmitter and receivers which excite and measure the energy of hydrogen atoms. The MRI room is a faraday cage which is made of copper and designed to shield out any external RF signals. The RF receivers are close to the head in order to have a better signal to noise ratio.

The first important component of the MRI scanner is a superconducting coil, in which electric currents can pass through with minimal resistance. When electric currents run through the coil, magnetic fields are created along the coil. The magnetic field passes through the bore of the scanner in which the subject is lying. Magnetic fields can affect different components of water molecules which are found within tissues. Protons on the hydrogen atom nucleus of water or fat behave like a magnet with a north pole and a south pole and usually these protons are randomly oriented. However, within the MRI bore, the protons align themselves along the magnetic field.

The second important element of the MRI scanner is the use of RF pulse to perturb and flip the alignment of the protons to be anti-parallel of the magnetic field. This process is called “excitation”. As the protons prefer to be aligned with the magnetic field, in time they will return into alignment in a process which is called “relaxation”. As the protons relax back to alignment from a high energy state

(deflected from magnetic field) to a low energy state (aligned with magnetic field), they release RF energy back which is captured by a radio receiver on the head coil. T1 is the time in which it takes for the proton to relax back into an aligned state. T1 is also called longitudinal relaxation as it is measured in parallel to the magnetic field (also known as spin lattice relaxation).

Protons have also a spin on the axis of the magnetic field. The spin is dependent on the strength of the magnetic field: proton within a weak magnetic field has a slow spin and proton within a strong magnetic field has a fast spin. In order for the proton to deflect from the aligned position, the RF pulse should have the same frequency as the spin of the proton (Larmor frequency), which only then can absorb the RF pulse. After deflection, the protons continue to spin but in the new direction which is out of alignment, and in a circular fashion around the magnetic field (precession - similar to a spin-top movement). However, not all of the protons have the same spin speed, and therefore, another process that is happening after the RF pulse is that protons de-phase from each other while they precess around the magnetic field. When the protons de-phase from each other over time, the RF signal decreases. T2 is the time that relates to the RF signal decrease because of de-phasing. T2 is also called transverse relaxation as it is measured perpendicular to the magnetic field (also known as spin-spin relaxation).

T1 and T2 produce different images, as T1 measures the speed of longitudinal relaxation and T2 measures the speed of dephasing, which are different components of different tissue types. Different tissues have different matrices of molecules with different interaction between protons which will result different T1 and T2 images for different tissue types. For example T1 relaxation of water will be longer than fat. Different pulse sequences have different qualities, as there are different ways to adjust the magnetic field between the RF pulse and RF energy measuring, and this will

emphasis different features of tissues. Different pulse sequences will have different functions which relate to which elements the researcher/physician wants to measure.

Besides the main coil which creates the main uniform magnetic field, three gradient coils are dispersed throughout the scanner in order to modify the magnetic field in the x, y and z planes (the sounds of the scanner results from adjusting the gradient coils). In order to get a 3D image of the brain, the magnetic field is designed to be different in different regions in the brain, which results different speeds of proton spin frequencies in different areas (stronger magnetic field = faster spin). As protons absorb only the RF pulse which match their spin frequency, not all of the protons will be deflected due to one specific RF pulse, and different RF pulses will deflect protons in different locations. This property is what allows 3D imaging, as the RF receiver can localize an area based on the spin frequency which spatially varies due to the gradient coils.

2.1.2 How Does fMRI Work?

Functional MRI (fMRI) is a non-invasive method which can measure temporal changes in brain metabolism which serve as a proxy for neural activity. fMRI is based on a version of T2 which is called T2* (Chavhan, et al., 2009). T2, which is the spin-spin relaxation, is the time of the dephasing of the protons after an RF pulse. While the protons dephase it is possible to give another 180° re-focusing pulse which flips their spin direction and instead of drifting apart (de-phasing), they drift back together (spin-echo (Hahn, 1950)). This re-focusing pulse is a way to reduce the T2 effect. However, some of the protons do not refocus after the 180° pulse and these correspond to T2*. The inability to refocus the phases completely arise from very small local distortions in the magnetic field (Schenck, 1996). fMRI utilize T2* as it is measuring distortions which are caused by iron in the hemoglobin in the blood. Hemoglobin has iron atoms that bind to oxygen, and this is how it supplies oxygen from the lungs to

the rest of the body. The magnetic field of the iron is dependent on the oxygen atom which is attached to it or not. After the oxygen has been delivered to the tissue, the hemoglobin becomes de-oxygenated (from oxyhemoglobin to deoxyhemoglobin). Deoxyhemoglobin is paramagnetic, while oxyhemoglobin is diamagnetic, and therefore deoxyhemoglobin creates a stronger magnetic field inhomogeneity which results a weaker signal. Therefore, the most popular fMRI method is named Blood-oxygen-level dependent (BOLD) (Bandettini, et al., 1992; Ogawa, et al., 1990). The change of intensity of the BOLD signal which relates to neural activity is usually less than 5%.

The relationship between BOLD signal and neural activity stems from neurovascular coupling and it is assumed that this relationship is linear (Heeger and Ress, 2002; Logothetis, et al., 2001). When activity of neurons increases so does the oxygen that is transported to these neurons; neural activity leads to oxygen consumption (Vanzetta and Grinvald, 1999), which leads to vasodilation and oversupply of oxygenated blood to the activated area (Buxton, et al., 1998; Fox and Raichle, 1986), the vasodilation results an increase in blood volume and decrease deoxyhemoglobin, which reduces the local magnetic field inhomogeneity and increases BOLD intensity. BOLD is a signal that is dependent on blood flow, blood volume and blood oxygenation.

The changes in blood vessels that result from neural activity does not happen immediately, but in a course of a number of seconds. The hemodynamic response function (HRF) describes how blood vessels change after neural activity. The average HRF peaks at around 6 seconds after the neural activity and this limits the affective temporal resolution of fMRI to about 2 seconds. The blood flow that results from neural activity spreads about 3mm around the location of the neural activity, and this limits the spatial resolution of fMRI. fMRI acquires a volume (3D image) once every

few seconds and so measures changes of activity in time. Using fMRI, it is possible to measure BOLD activity that correspond to an experimental manipulation, and it is possible to measure different properties of spontaneously fluctuating BOLD activity at so called 'rest'.

2.1.3 Resting State Functional Connectivity (RSFC)

RSFC is a method that is used to measure co-activation of different regions in the brain without any tasks (Biswal, et al., 1995). At so called resting state, different regions in the brain have different activation patterns. The connectivity of each area in the brain can be plotted in time and correlated with another area in the brain. The correlation between these two areas is called RSFC, and it measures the co-activation of these areas. There are two main ways to analyze RSFC. The first is to choose a region of interest (ROI) and measures RSFC with other regions in the brain. The other method is to decompose the brain BOLD signal into resting state networks (RSN) using independent component analysis (ICA).

When analyzing RSFC of an ROI to the rest of the brain, what calculated is how the time course of this ROI (seed) can predict time courses of other regions in the brain. To do so, the activity in time of this ROI is plotted (an average of all of the voxels in the ROI, for each acquired volume). The time course of this ROI is used as a predictor in a general linear model (GLM) which attempt to predict all other voxels. The beta weights (β) that result from the GLM are the estimate of how well the ROI time course fits the time course of other voxels.

The other main method to analyze RSFC, is to separate the whole brain BOLD signal into RSNs, using ICA (Beckmann, et al., 2005; Smith, et al., 2009). ICA is a method that separates a multivariate signal into subcomponents which are independent from

each other. By doing so, ICA identify networks of regions which tend to be activated together, but are not necessarily near each other. These networks are called RSNs. The most famous RSN is probably the default mode network (DMN) which is a network that is activated in task-negative conditions, and is associated with self-related processes (Raichle, 2015).

2.2 Procedure for LSD Study

2.2.1 Study Approvals

This study was approved by the National Research Ethics Service committee London-West London and was conducted in accordance with the revised declaration of Helsinki (2000), the International Committee on Harmonization Good Clinical Practice guidelines, and National Health Service Research Governance Framework. Imperial College London sponsored the research, which was conducted under a Home Office license for research with schedule 1 drugs.

2.2.2 Participants

All participants were recruited via word of mouth and provided written informed consent to participate after study briefing and screening for physical and mental health. The screening for physical health included electrocardiogram (ECG), routine blood tests, and urine test for recent drug use and pregnancy. A psychiatric interview was conducted and participants provided full disclosure of their drug use history. Key exclusion criteria included: < 21 years of age, personal history of diagnosed psychiatric illness, immediate family history of a psychotic disorder, an absence of previous experience with a classic psychedelic drug (e.g. LSD, mescaline, psilocybin/magic mushrooms or DMT/ayahuasca), any psychedelic drug use within 6 weeks of the first scanning day, pregnancy, problematic alcohol use (i.e. > 40 units

consumed per week), or a medically significant condition rendering the volunteer unsuitable for the study.

2.2.3 Study Setting and Overview

Screening took place at Imperial's clinical research facility (ICRF) at the Hammersmith hospital campus. All study days were performed at Cardiff University Brain Research Imaging Centre (CUBRIC). Participants who were found eligible for the study attended two study days that were separated by at least 14 days. On one day, the participants received placebo, and on the other day they received LSD. The order of the conditions was balanced across participants, and participants were blind to this order but the researchers were not.

On scanning days, volunteers arrived at the study centre at 8:00am. They were briefed in detail about the study day schedule, gave a urine test for recent drug use and pregnancy, and carried out a breathalyser test for recent alcohol use. A cannula was inserted into a vein in the antecubital fossa by a medical doctor and secured. The participants were encouraged to close their eyes and relax in a reclined position when the drug was administered. All participants received 75 µg of LSD, administered intravenously via a 10ml solution infused over a two minute period, followed by an infusion of saline. The administration was followed by an acclimatization period of approximately 60 minutes, in which (for at least some of the time) participants were encouraged to relax and lie with their eyes closed inside a mock MRI scanner. This functioned to psychologically prepare the participants for being in the subsequent (potentially anxiogenic) MRI scanning environment.

Participants reported noticing subjective drug effects between 5 to 15 minutes post-dosing, and these approached peak intensity between 60 to 90 minutes post-dosing. The duration of a subsequent plateau of drug effects varied among individuals but was generally maintained for approximately four hours post-dosing. MRI scanning started approximately 70 minutes post-dosing, and lasted for approximately 60

minutes. This included a structural scan, arterial spin labelling (ASL) fMRI, and BOLD fMRI. After the MRI scanning, there was a break of approximately 35 minutes, after which MEG scanning was performed. Once the subjective effects of LSD had sufficiently subsided, the study psychiatrist assessed the participant's suitability for discharge.

2.2.4 Scanning Design and Content

BOLD scans consisted of three eyes-closed resting state scans, each lasting seven minutes. After each seven minute scan, VAS ratings were performed in the scanner via a response-box. The first and third scans were eyes-closed rest but the second scan also incorporated listening to some music. This component of the study is reported elsewhere (Kaelen, et al., 2016). Prior to each scan, participants were instructed via onscreen instructions to close their eyes and relax. Participants also performed a retinotopic localization paradigm at the end of the scanning session. This component of the study is reported in more details in section 2.5.5 of this thesis and in Roseman, et al. (2016).

2.3 Procedure for Psilocybin Study

Psilocybin data was acquired in an earlier study (Carhart-Harris, et al., 2012a). It was used in this thesis as a replication data for chapter 3, and in chapter 5.

2.3.1 Study Approvals

The study was approved by a local NHS Research Ethics Committee and Research and Development department, and conducted in accordance with Good Clinical Practice guidelines. A Home Office Licence was obtained for storage and handling of a Schedule 1 drug. The University of Bristol sponsored the research.

2.3.2 Participants

All participants gave informed consent to participate in the study. A physical examination, including electrocardiogram (ECG), routine blood tests, and urine test for drugs of abuse and pregnancy were carried out. A psychiatric assessment was conducted and participants disclosed their drug taking histories. Exclusion criteria were: less than 21 y of age, pregnancy, personal or immediate family history of psychiatric disorder, substance dependence, cardiovascular disease, claustrophobia, blood or needle phobia, or a significant adverse response to a hallucinogenic drug. All subjects had previous experience with a hallucinogenic drug but not within 6 wk of the study.

2.3.3 Study Setting and Design

All subjects underwent two 12-min eyes-closed resting-state BOLD fMRI scans on 2 separate occasions at least 7 days apart: placebo (10ml saline, 60-s intravenous injection) was given on 1 occasion and psilocybin (2mg dissolved in 10ml saline) on the other. Seven of the subjects received psilocybin in scan 1, and 8 received it in scan 2. Injections were given manually by a study doctor situated within the scanning suite. The 60-s infusions began exactly 6min after the start of the 12-min scans. The subjective effects of psilocybin were felt almost immediately after injection and were sustained for the duration of the scan. The data used in chapter 3 was from the end of the infusion to the end of the scan (5 minutes of BOLD data). The data used in chapter 5 was from the beginning of the infusion to 3 minutes after the beginning of infusion (onset of drug effects).

2.4 Subjective Measures - LSD

2.4.1 Altered States of Consciousness Questionnaire (ASC)

The Altered State of Consciousness questionnaire (ASC) (Dittrich, 1975; Dittrich, 1998; Studerus, et al., 2010) was rated by the end of the day and referred retrospectively to the peak drug effects, which coincided with the fMRI session. ASC can be divided to 5 dimensions (Dittrich, 1998) (94 items), or 11 dimensions (Studerus, et al., 2010) (42 items). The 5 dimensions are: *oceanic boundlessness* (OBN), *dread of ego dissolution* (DED), *visionary restructuralization* (VRS), *auditory alterations* (AUA) and *vigilance reduction* (VIR) (n.b. translation from the German original may explain the slightly peculiar choice of terms e.g. ‘visionary restructuralization’). The 11 sub-dimensions are made only from OBN, DED and VRS. The OBN sub-dimensions are *experience of unity*, *spiritual experience*, *blissful state*, *insightfulness*, and *disembodiment*. The DED sub-dimensions are *impaired control or cognition*, and *Anxiety*. The VRS sub-dimensions are *complex imagery*, *elementary imagery*, *audio/visual synesthesia*, and *changed meaning of percepts*. ASC ratings were only included from the 15 participants who featured in the fMRI analyses (Figure 2.1). For the purpose of this thesis, the dimensions of interest were *VRS* and its sub-dimensions *complex imagery* and *simple imagery* (see section 7.7 for limitation of ASC visual dimensions). The ratings of the three dimensions of interest, from the 15 subjects that were used for fMRI analysis, are as follow (placebo mean rating, LSD mean rating, p value from a 2-tail t-test; range = 0-100): *VRS* (3.5 ± 11.7 , 51.4 ± 26.4 , $p < 0.0001$), *Simple Imagery* (5.6 ± 19.4 , 70.9 ± 32.9 , $p < 0.0001$), *Complex Imagery* (2.7 ± 7.4 , 44.8 ± 29.2 , $p < 0.0001$).

2.4.2 In-Scanner Ratings

In scanner, VAS ratings were obtained after each scan. The scales included items for intensity, simple imagery, complex imagery, positive mood, ego dissolution and emotional arousal (Table 2.1). Specifically, they were phrased as follows: 1) “Please rate the intensity of the drug effects during the last scan”, with a bottom anchor of “no effects”, a mid-point anchor of “moderately intense effects” and a top anchor of

“extremely intense effects”; 2) “With eyes closed, I saw patterns and colours”, with a bottom anchor of “no more than usual” and a top anchor of “much more than usual”; 3) “With eyes closed, I saw complex visual imagery”, with the same anchors as item 2; 4) “How positive was your mood for the last scan?”, with the same anchors as item 2, plus a mid-point anchor of “somewhat more than usual”; 5) “I experienced a dissolving of my self or ego”, with the same anchors as item 2; and 6) “Please rate your general level of emotional arousal for the last scan”, with a bottom anchor of “not at all emotionally aroused”, a mid-point anchor of “moderately emotionally aroused” and a top anchor of “extremely emotionally aroused”. The questions of interest for this thesis are the simple imagery (“With eyes closed, I saw patterns and colours”) and complex imagery (“With eyes closed, I saw complex visual imagery”).

VAS Ratings		End of ASL scans (100 mins post inj.)	End of BOLD scans (135 mins post inj.)	End of EC MEG scans (225 mins post inj.)
LSD (mean + SEM)	Intensity	11.7 (0.8)	12.4 (0.9)	6.6 (0.8)
	Simple hallucinations	10.4 (1.7)	9.9 (1.5)	6.5 (1.3)
	Complex hallucinations	8.0 (1.6)	7.4 (1.7)	4.3 (1.1)
	Emotional arousal	10.6 (0.9)	11.2 (1.2)	6.4 (1)
	Positive mood	7.8 (1.4)	7.0 (1.5)	5.3 (1)
	Ego-dissolution	4.4 (1.3)	5.7 (1.7)	3.3 (1.1)
Placebo (mean + SEM)	Intensity	0.2 (1.8)	0.2 (0.15)	0.17 (0.14)
	Simple hallucinations	0.17 (0.1)	0.17 (1.0)	0.1 (0.04)
	Complex hallucinations	0.1 (0.9)	0.03 (0.03)	0 (0)
	Emotional arousal	0.9 (0.3)	0.8 (0.3)	0.8 (0.35)
	Positive mood	0.7 (0.3)	0.3 (0.15)	0.4 (0.25)
	Ego-dissolution	0.2 (0.2)	0 (0)	0 (0)

Table 2.1. VAS ratings

Mean values (possible range = 0-20) and positive standard errors for VAS ratings completed at 3 different time points post LSD and placebo injection. See “subjective ratings” below for more details regarding the items. Ratings were visually presented after each scan (on a projection screen visible from within the scanner) and completed

via button press. All items, in all 3 modalities, were rated significantly higher under LSD than placebo ($p < 0.05/6$, Bonferonni corrected). EC = eyes closed.

Altered states of consciousness (ASC) questionnaire

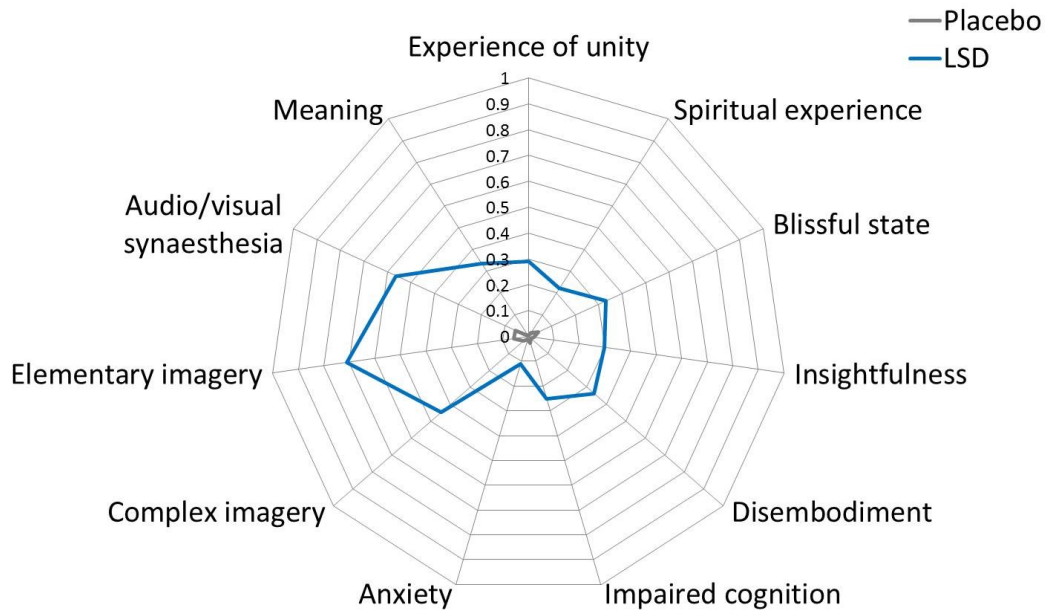


Figure 2.1. Altered State of Consciousness questionnaire

The 11 factor ASC was completed at the end of scanning days and is presented here as a radar plot with mean total values (0-1) for the LSD (blue) and placebo conditions (gray). Ten of the 11 factors were rated significantly higher under LSD than placebo ($p < 0.05/11$, Bonferonni corrected), with “anxiety” as the exception.

2.5 fMRI parameters

The following parameters and analysis procedures apply generally to all chapters of the thesis, with some specific variations for each chapter. The LSD and psilocybin data were acquired in Cardiff University Brain Research Imaging Centre (CUBRIC).

2.5.1 Anatomical Scans

LSD and Psilocybin: Imaging was performed on a 3T GE HDx system. These were 3D fast spoiled gradient echo scans in an axial orientation, with field of view = $256 \times 256 \times 192$ and matrix = $256 \times 256 \times 192$ to yield 1mm isotropic voxel resolution. TR/TE = 7.9/3.0ms; inversion time = 450ms; flip angle = 20° .

2.5.2 BOLD fMRI Data Acquisition

LSD: Two BOLD-weighted fMRI data were acquired using a gradient echo planar imaging sequence, TR/TE = 2000/35ms, field-of-view = 220mm, 64×64 acquisition matrix, parallel acceleration factor = 2, 90° flip angle. Thirty-five oblique axial slices were acquired in an interleaved fashion, each 3.4mm thick with zero slice gap (3.4mm isotropic voxels). The precise length of each of the two BOLD scans was 7:20 minutes.

Psilocybin: BOLD-weighted fMRI data was acquired using a gradient echo planar imaging sequence, TR/TE = 3000/35ms, field-of-view = 192 mm, 64×64 acquisition matrix, parallel acceleration factor = 2, 90° flip angle. Fifty-three oblique-axial slices were acquired in an interleaved fashion, each 3 mm thick with zero slice gap (3mm isotropic voxels). The BOLD scan began 6 minutes before infusion of psilocybin. The BOLD data used for chapter 3 was from 1 minute after infusion (from the end of 60 seconds infusion) to 6 minutes after infusion (total of 5 minutes, 100 TRs). The BOLD

data used for chapter 5 was from infusion time to 3 minutes after beginning of infusion (onset phase, total of 3 minutes, 60 TRs).

2.5.3 BOLD Pre-processing

LSD: Four different but complementary imaging software packages were used to analyze the fMRI data. Specifically, FMRIB Software Library (FSL) (Smith, et al., 2004), AFNI (Cox, 1996), Freesurfer (Dale, et al., 1999) and Advanced Normalization Tools (ANTs) (Avants, et al., 2009) were used. One subject did not complete the BOLD scans due to anxiety and an expressed desire to exit the scanner and four others were discarded from the group analyses due to excessive head movement. Principally, motion was measured using frame-wise displacement (FD) (Power, et al., 2014). The criterion for exclusion was subjects with >15% scrubbed volumes when the scrubbing threshold is $FD = 0.5$. After discarding these subjects we reduced the threshold to $FD = 0.4$. The between-condition difference in mean FD for the 4 subjects that were discarded was 0.323 ± 0.254 and for the 15 subjects that were used in the analysis the difference in mean FD was 0.046 ± 0.032 . The following pre-processing stages were performed (more details about the rational for each pre-processing stage could be found in the next section, "Motion Correction"): 1) removal of the first three volumes; 2) de-spiking (3dDespike, AFNI); 3) slice time correction (3dTshift, AFNI); 4) motion correction (3dvolreg, AFNI) by registering each volume to the volume most similar, in the least squares sense, to all others (in-house code); 5) brain extraction (BET, FSL); 6) rigid body registration to anatomical scans (twelve subjects with FSL's BBR, one subject with Freesurfer's bbrregister and two subjects manually); 7) non-linear registration to 2mm MNI brain (Symmetric Normalization (SyN), ANTs) (for chapter 4, this step did not take place and analysis was done in native space); 8) scrubbing (Power, et al., 2012) - using an FD threshold of 0.4 (the mean percentage of volumes scrubbed for placebo and LSD was $0.4 \pm 0.8\%$ and $1.7 \pm 2.3\%$, respectively). The maximum number of scrubbed volumes per scan was 7.1%) and scrubbed volumes were replaced with the mean of the surrounding volumes. Additional pre-

processing steps included: 9) spatial smoothing (FWHM) of 6mm (3dBlurInMask, AFNI) for chapter 3, and no smoothing for chapter 4; 10) band-pass filtering between 0.01 to 0.08 Hz (3dFourier, AFNI); 11) linear and quadratic de-trending (3dDetrend, AFNI); 12) regressing out 9 nuisance regressors (all nuisance regressors were bandpassed filtered with the same filter as in step 10, out of these, 6 were motion-related (3 translations, 3 rotations) and 3 were anatomically-related (not smoothed). Specifically, the anatomical nuisance regressors were: I) ventricles (Freesurfer, eroded in 2mm space), II) draining veins (DV) (FSL's CSF minus Freesurfer's Ventricles, eroded in 1mm space) and III) local white matter (WM) (FSL's WM minus Freesurfer's subcortical grey matter (GM) structures, eroded in 2mm space). Regarding local WM regression, AFNI's 3dLocalstat was used to calculate the mean local WM time-series for each voxel, using a 25mm radius sphere centered on each voxel (Jo, et al., 2010).

Psilocybin: The same preprocessing pipeline was applied for psilocybin for chapter 3. For chapter 5, highpass filter was not applied; detrending was not applied; and head motion time course derivatives were used as nuisance regressors instead of head motion time courses. Six subjects were discarded due to excessive head motion. The between-condition difference in mean FD for the 6 subjects that were discarded was 0.257 ± 0.053 and for the 9 subjects that were used in the analysis the difference in mean FD was 0.024 ± 0.055 . For the 9 subjects used in this analysis, the mean percentage of volumes scrubbed (FD = 0.4) for placebo and psilocybin was $0.8 \pm 1.6\%$ and $0.2 \pm 0.4\%$, respectively. The maximum number of scrubbed volumes per scan was 4%.

2.5.4 Motion Correction

After discarding four subjects due to head motion, fifteen were left for the BOLD analysis of LSD. There was still a significant between-condition difference in motion for these subjects however (mean FD of placebo = 0.074 ± 0.032 , mean FD of LSD = 0.12 ± 0.05 , $p = 0.0002$). For psilocybin, 9 subjects were left for analysis and there was

no significant difference in head motion between conditions (mean FD of placebo = 0.086 ± 0.042 , mean FD of psilocybin = 0.11 ± 0.029 , $p = 0.094$, 1-tail t-test). RSFC analysis is extremely sensitive to head motion (Power, et al., 2014) and therefore special consideration was given to the pre-processing pipeline to account for motion. This section goes into more detail about the pre-processing steps that were performed to reduce artefacts associated with motion as well as other non-neural sources of noise.

De-spiking has been shown to improve motion-correction and create more accurate FD values (Jo, et al., 2013) and low-pass filtering at 0.08 Hz has been shown to perform well in removing high frequency motion (Satterthwaite, et al., 2013). Six motion regressors were used as covariates in linear regression. It was decided that using more than six (e.g., “Friston 24-parameter motion regression” (Friston, et al., 1996)) would be redundant and may impinge on neural signal (Bright and Murphy, 2015) (especially when other rigorous processes such as scrubbing (Power, et al., 2012) and local WM were applied (Jo, et al., 2010)). Using anatomical regressors is also a common step to clean noise and ventricles, DV and local WM were used in the pipeline employed in the present analyses. Local WM regression has been suggested to perform better than global WM regression (Jo, et al., 2013).

It has previously been shown that head motion biases functional connectivity results in a distance-dependent manner (Power, et al., 2014). Therefore, as a quality control step, at the end of the pre-processing procedure, cloud plots were constructed to test for relationships between inter-node Euclidian distance and correlations between FD and RSFC across subjects. In cases in which motion is affecting the results, proximal nodes will have high FD-RSFC correlations and distal nodes will have low FD-RSFC correlations. This would result in a negative correlation between distance and FD-RSFC correlation. In the present dataset, the distance to FD-RSFC correlation was very close to zero for both the placebo and LSD conditions (Figure 2.3), suggesting that the extensive pre-processing measures had successfully controlled for distance-related motion artefacts.

2.5.5 Retinotopic Localizer

Subjects were presented with a 4 min 24 sec video that alternated between vertical and horizontal polar angles (8 cycles, resolution = 1400 x 1050, visual angle = 23 x 23°, TR/TE = 2000/25ms, 3 mm isotropic voxels). The wedge consisted of a colored checkerboard with superimposed moving black and white faces (from FERET database (Phillips, et al., 1998)) and coherently moving white dots - new flow every 0.5 sec. Fourier analysis with two distinct conditions was performed on the placebo data to identify activity corresponding to the vertical and horizontal polar angles (Sereno, et al., 1995). Borders between V1, V2 and V3 were identified manually for each subject (using an in-house program). The middle of the vertical meridian activation was used to mark the border between V1 and V2 and the middle of the horizontal meridian to mark the border between V2 and V3. The retinotopic localizer took place after the resting-state scans in order to avoid a possible effect of the retinotopic localizer on the resting-state scans (Albert, et al., 2009; Hasson, et al., 2009; Waites, et al., 2005). The retinotopic localizer took place for both placebo and LSD sessions. However, the BOLD data from the localizer of the LSD session was noisier due to head-motion, and do to inability of subjects to concentrate and focus on the center as reported by many subjects during the interviews. Therefore, the retinotopic patches were identified solely on the placebo session.

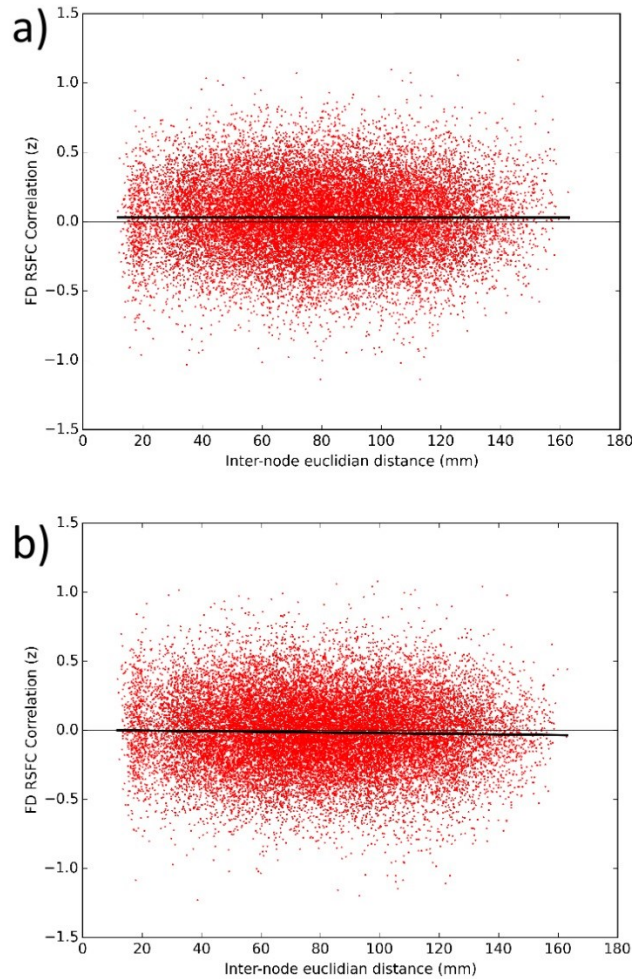


Figure 2.3. Head Motion Cloud Plots

Correlation between inter-node Euclidian distance (mm) and FD-RSFC correlation (r) for both LSD (a) and placebo (b) after pre-processing. Nodes were defined using the Craddock atlas with 240 parcellations, excluding supplementary motor and motor areas. For each pair of nodes, RSFC was calculated with pearson's r and transformed into z using fisher's transformation. For each pair of nodes, a correlation across subjects was calculated between mean FD and RSFC (r) and transformed into z using fisher's transformation. This correlation is plotted against the distance between nodes (mm). The correlations for LSD and placebo were $r = -0.0009$ ($p = 0.089$) and $r = -0.025$ ($p < 0.001$), respectively, suggesting that motion did not affect RSFC in a distant dependent manner after pre-processing.

“Funny, I'd forgotten that what comes to you when you take a psychedelic is not always a revelation of something new and startling; you're more liable to find yourself reminded of simple things you know and forgot you knew - seeing them freshly - old, basic truths that long ago became cliches, so you stopped paying attention to them.”

— Ann Shulgin

3. STUDY 1 |

V1 RSFC

3.1 Introduction

This chapter focuses on communication patterns between V1 and the rest of the brain. V1 connectivity is measured using RSFC which reveals co-activation of V1 with other regions. From this co-activation, one can imply that regions that are active together are functionally connected to each other and to some extent work together to process information. Based on previous research that shows the involvement of V1 in psychedelic imagery (chapter 1.8), it was hypothesized that V1 will show increased RSFC with other cortical and subcortical regions under LSD, and that this increase in RSFC will correlate with subjective ratings. Furthermore, it was hypothesized that increases in V1 RSFC will correlate with decreased alpha power, which is the signature neural correlate of psychedelic imagery (see more on alpha power in section 1.8.4).

I was also interested in predicting subjective response for LSD using baseline (placebo) subject specific features of alpha frequency. I hypothesized that subjects that had a larger decrease in alpha power between eyes closed and eyes open, or video, will have a larger decrease in alpha power under LSD (LSD eyes closed vs. placebo eyes closed), and will have stronger subjective imagery rating.

RSFC was chosen over other resting state methods such as ICA as the former is more accurate in measuring small brain regions of interest while the latter better in investigating large scale brain network, and in this analysis we chose to focus on

visual subregions which can be localized for each subject based on their brain activity (see method below), but cannot be accurately identified using ICA.

3.2 Methods

Design and fMRI parameters are described in more details in chapter 2.

Seed-based RSFC

Based on prior hypotheses, V1 was chosen for this analysis as the prime ROI of interest. V2 and V3 were chosen as secondary analysis. ROIs (V1, V2, and V3) were localized for each subject using a modified retinotopic scan. Mean time-series were derived for each ROI for each resting state scan. The time series were derived from unsmoothed data since it was based on a functional localizer acquired in the subject's native space. RSFC analysis was performed using FSL's FEAT. Pre-whitening (FILM) was applied to correct for auto correlations. A fixed-effects general linear model (GLM) was used to combine the results of both resting state scans (2 scans x 7 mins) within a session. Subsequently, a higher-level analysis was performed to compare placebo versus LSD conditions using a mixed-effects GLM (FLAME 1), cluster corrected ($z > 2.3$, $p < 0.05$). MRICron was used to display the results. Psilocybin dataset was used to replicate this result. As there was no retinotopic scan in the psilocybin study, V1 seed was chosen based on Juelich atlas (threshold 70).

MEG acquisition

Data from 13 volunteers were suitable for the MEG analyses. For each condition (placebo and LSD) there were two 7 minutes resting state with eyes closed scans, two

7 minutes resting state with eyes open, and one 7 minute video-watching scan. The relevant data were acquired ~50 min after completion of the MRI protocol. Data was filtered into the alpha frequency (8-15Hz) and averaged within occipital sensors only. Detailed information can be found in Carhart-Harris, et al. (2016a). Participants lay in supine position and whole-head MEG recordings were made using a CTF 275-channel radial gradiometer system sampled at 1200 Hz (0–300 Hz band-pass). An additional 29 reference channels were recorded for noise cancellation purposes and the primary sensors were analyzed as synthetic third-order gradiometers. Four of the 275 channels were turned off due to excessive sensor noise. In addition to the MEG channels, participants' ECG was recorded: horizontal and vertical electro-oculograms as well as electromyograms from bilateral frontalis and temporalis muscles. Continuous monitoring of participant head position was employed using three fiducial coils (nasion and pre-auricular points).

MEG Preprocessing

All MEG recordings were initially high-pass filtered at 1 Hz, and segmented into epochs of 2 s in length (210 epochs). Each epoch was then visually inspected, and those with gross artifacts (e.g., head movements, jaw clenches) were removed from the analysis. An automated algorithm was used to remove further epochs contaminated with muscle artefacts. In this algorithm, a set of 30 gradiometer sensors were predefined at the edge of the MEG dewar, as these are most likely to be contaminated by muscle artefacts (Muthukumaraswamy, et al., 2015). Using Hanning-windowed fourier transformations, the mean spectral power was calculated for these sensors in the 105-145Hz frequency band for each epoch. If the resulting power averaged across these sensors exceeded 10 fT (Muthukumaraswamy, et al., 2015) then that epoch was eliminated from subsequent analysis. ICA was performed on the remaining epochs as implemented in Fieldtrip/EEGLAB (Delorme and Makeig, 2004; Oostenveld, et al., 2011) to identify and remove ocular, muscle and cardiac artifacts from the data. Any components that showed a correlation ($r > .10$) in the

time domain with the EOG/EMG electrodes were automatically removed. Likewise, any components that showed correlations ($r > .10$) with similarly filtered EOG/EMG channels after being bandpass filtered in the range 105-145 Hz were removed. Visual inspection was also used to remove artifact components. All subsequent sensor space analysis was performed on the ICA cleaned datasets. Of the twenty participants, one was unable to complete both sessions and a further five were discarded due to the presence of excessive muscle artefacts that could not be satisfactorily removed by ICA, or due to excessive head motion. Out of these subjects, only 13 had reliable BOLD data as well. Therefore, correlations between BOLD changes and alpha power are based only on 13 subjects.

Alpha power in occipital sensors

Using the FieldTrip toolbox (Oostenveld, et al., 2011), MEG data was converted to planar gradient configuration and then conducted a frequency analysis of the individual vector directions. Frequency analysis was conducted using Hanning windowed fast Fourier transforms between 8 and 15 Hz at 0.5 Hz frequency intervals. Average power across all occipital sensors was calculated to give occipital alpha power. A relatively high upper alpha frequency cut-off (15 Hz) was used as preliminary analyses revealed a striking peak shift in the alpha-band frequency (Carhart-Harris, et al., 2016a). The difference between placebo and LSD was calculated as $\log(LSD/Placebo)$. Paired t-test was used to measure the significance of the difference between LSD and placebo, for eyes closed, eyes open, and while watching a video.

It was hypothesized that the normal baseline activity of alpha power (placebo) can predict sensitivity to LSD. The differences of occipital alpha power between eyes closed and eyes open ($\log(open/closed)$), and between eyes closed and video ($\log(video/closed)$), under placebo, were correlated with peak subjective LSD

experience measured with ASC (simple and complex imagery), and were correlated with eyes closed changes in occipital alpha power between LSD and placebo.

3.3 Results

Seed-based RSFC

Data from 15 volunteers were suitable for the BOLD analysis (four females; mean age, 30.5 ± 8.0 y). Analyses revealed increased RSFC between V1 and a large number of cortical and subcortical brain regions (Figure 3.1 and Table 3.1). Unthresholded maps can be viewed in Neurovault (Gorgolewski, et al., 2015) (neurovault.org/collections/FBVSAVDQ/). Increased V1 RSFC (to the most significant regions presented in Figure 3.5 ($p < 0.01$, 5,000 permutations) correlated with VAS ratings of simple hallucinations ($r = 0.62$, $p = 0.012$, $p_{\text{bonferroni}} = 0.048$) as well as ASC ratings of elementary imagery ($r = 0.63$, $P = 0.012$, $p_{\text{bonferroni}} = 0.048$) and complex imagery ($r = 0.74$; $p = 0.0016$, $p_{\text{bonferroni}} = 0.006$). These correlations were specific to the visual dimensions of VAS and ASC compared to other dimensions (Table 3.2). Furthermore, increased RSFC of V2 and V3 was observed as well (Figure 3.2 and Figure 3.3, respectively). It can be seen that the results of V2 and V3 are in the same direction as V1 but less pronounced, this might be due to difference in the placebo condition of V2 and V3 which is already more connected to higher level areas. Replication of V1 RSFC with psilocybin can be observed (Figure 3.4). The direction of the result is similar to LSD, but less pronounced (the reason for that might be the weaker statistical power of the psilocybin data set (less subjects, only one scan per subject, and less TRs)).

Occipital Alpha Power

Occipital alpha power decreased significantly under LSD vs. placebo for resting state eyes closed, eyes open, and video watching ($p = 0.01$, $p = 0.02$, and $p = 0.05$, respectively, 2-tail paired t-test). The occipital alpha power decrease (from placebo to LSD) with eyes closed correlated significantly with in-scanner subjective measures of simple imagery ($r = -0.61$, $p = 0.012$, 1-tail) and marginally significant with complex

imagery ($r = -0.47$, $p = 0.053$, 1-tail). Furthermore, occipital alpha power decreases significantly correlated with increased V1 RSFC ($r = -0.61$, $p = 0.013$, 1-tail). No significant correlations were found between occipital alpha power decreases in different conditions under placebo, and simple and complex imagery rating under LSD, nor with alpha power changes between LSD and placebo.

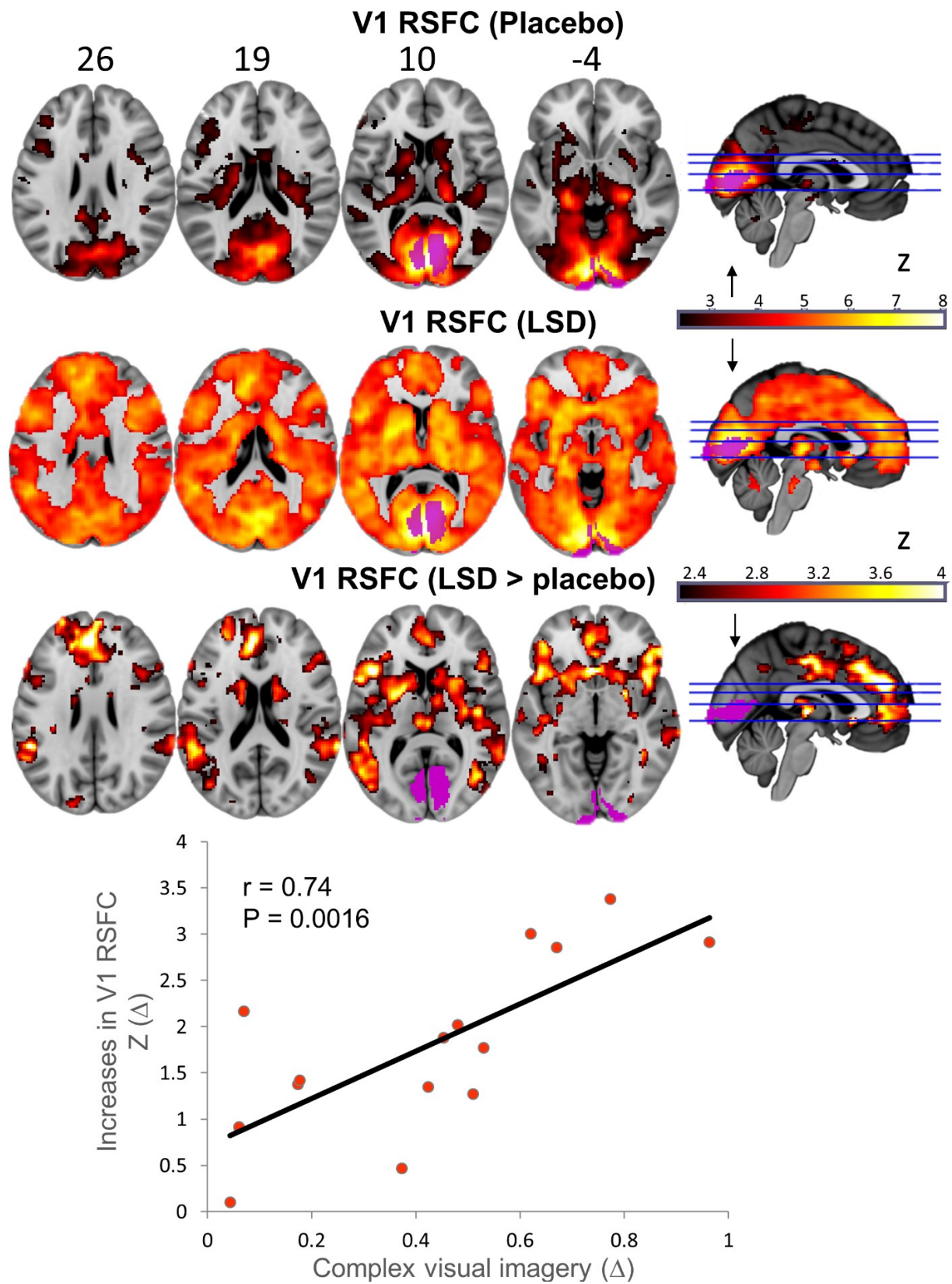


Figure 3.1. V1 RSFC

Significant between-condition differences (orange = increases) in RSFC between the V1 seed region (purple, for illustration purposes only, as seed was localized for each subject based on retinotopic scan) and the rest of the brain. Unthresholded maps can be viewed in neurovault.org/collections/FBVSAVDQ/ (n = 15). Correlation between mean Z values of increased V1 RSFC (Figure 3.5) and complex imagery is presented at the bottom of the figure.

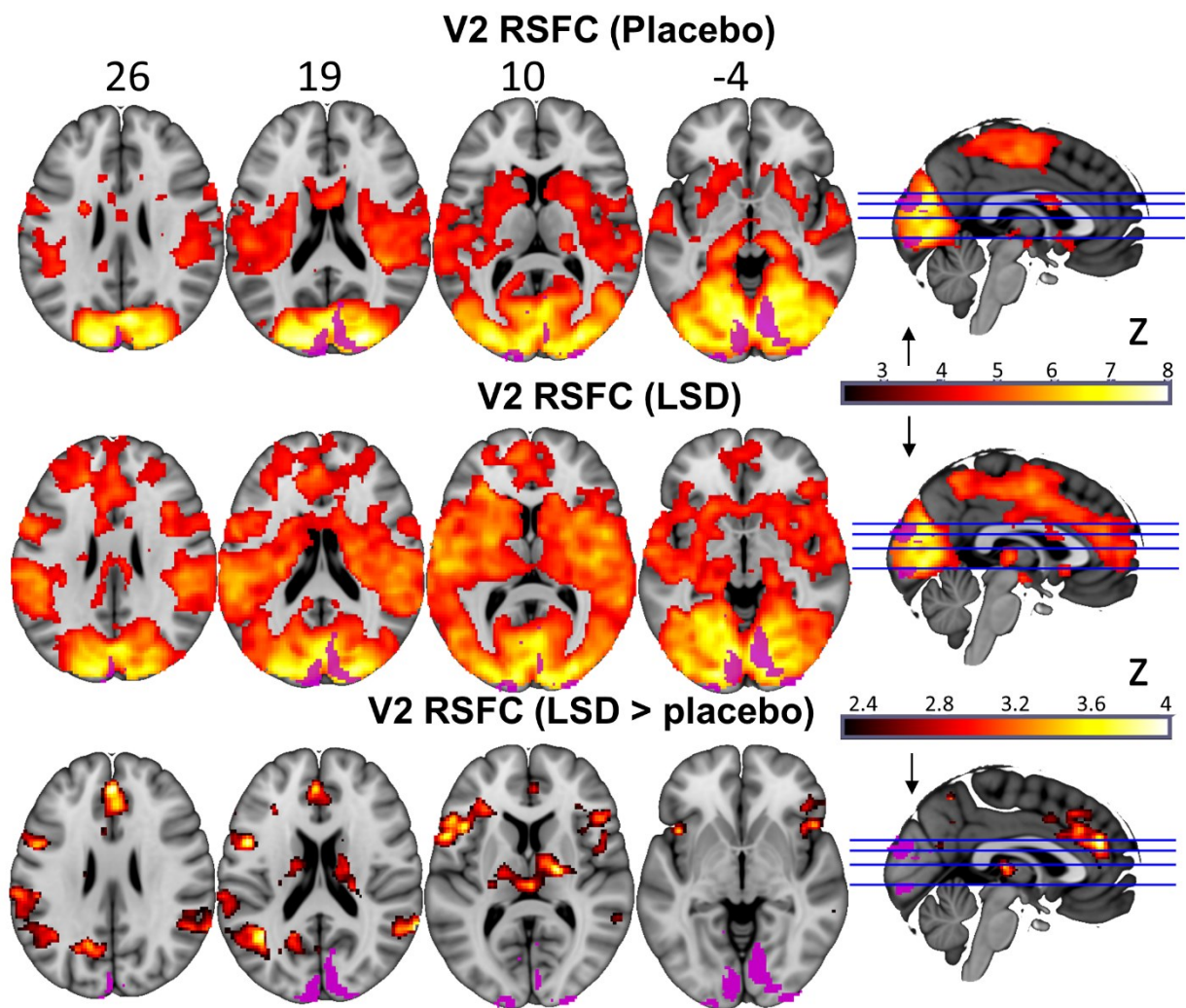


Figure 3.2. V2 RSFC

Significant between-condition differences (orange = increases) in RSFC between the V2 seed region (purple, for illustration purposes only, as seed was localized for each subject based on retinotopic scan) and the rest of the brain.

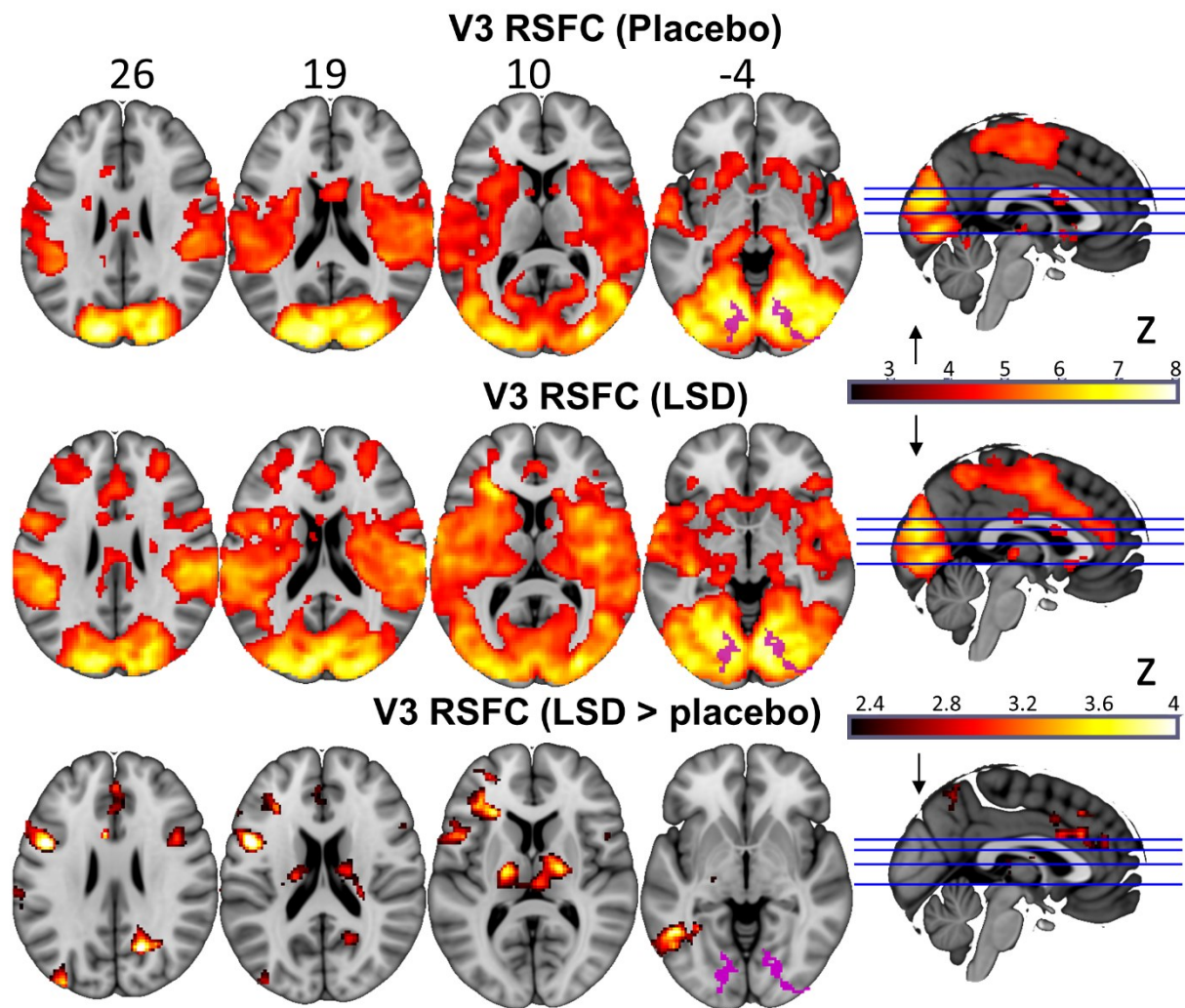


Figure 3.3. V3 RSFC

Significant between-condition differences (orange = increases) in RSFC between the V3 seed region (purple, for illustration purposes only, as seed was localized for each subject based on retinotopic scan) and the rest of the brain.

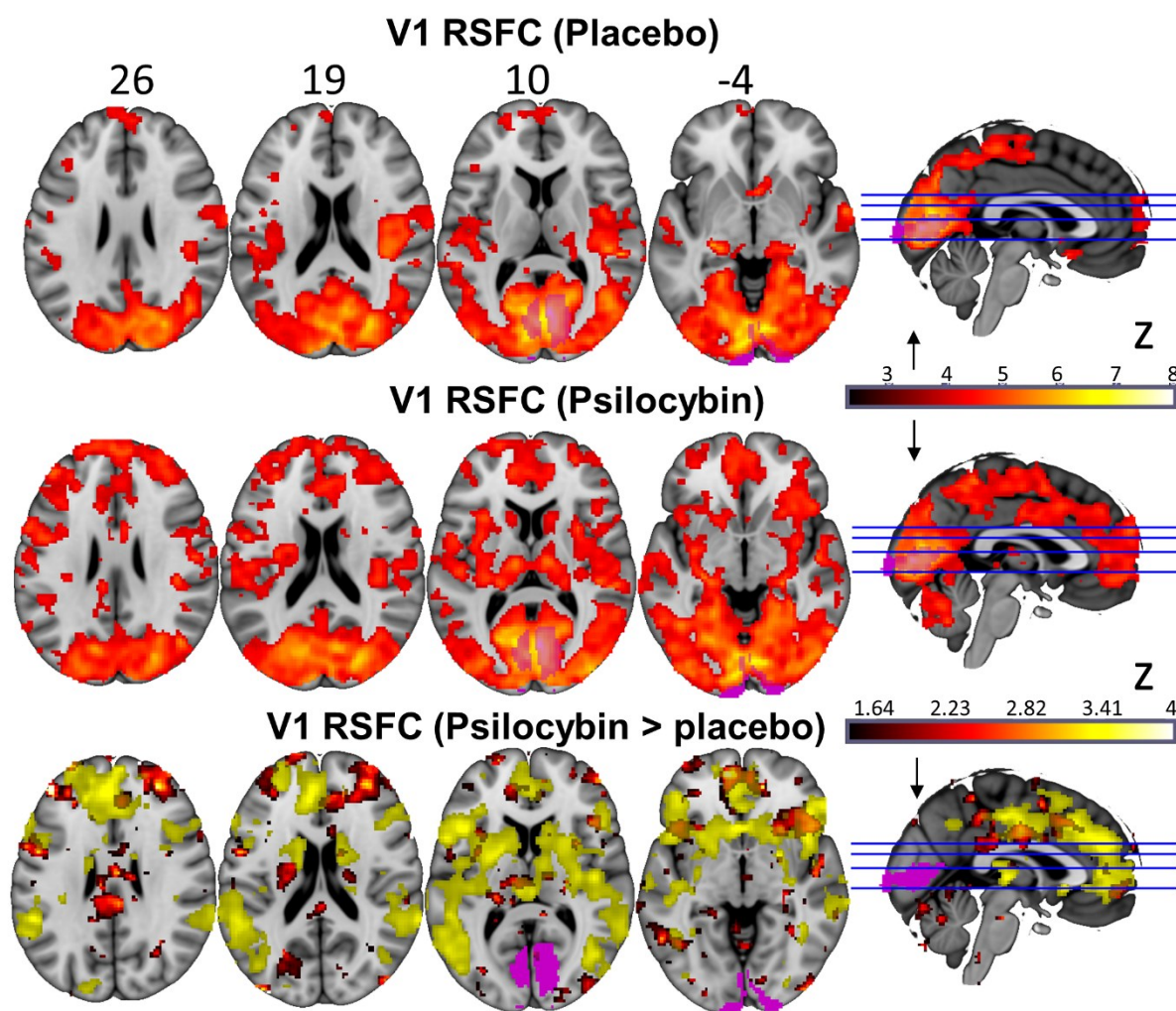


Figure 3.4. V1 RSFC, psilocybin

Replication with psilocybin of V1 RSFC LSD connectivity. Significant between-condition differences (orange = increases) in RSFC between the V1 seed region (purple) and the rest of the brain. In yellow are the regions that showed increased V1 RSFC with LSD (Figure 3.1). Increased RSFC of psilocybin is layered on top of yellow regions. Similarities are observed between psilocybin and LSD, however the result with LSD showed stronger increases (maybe due to stronger statistical power).

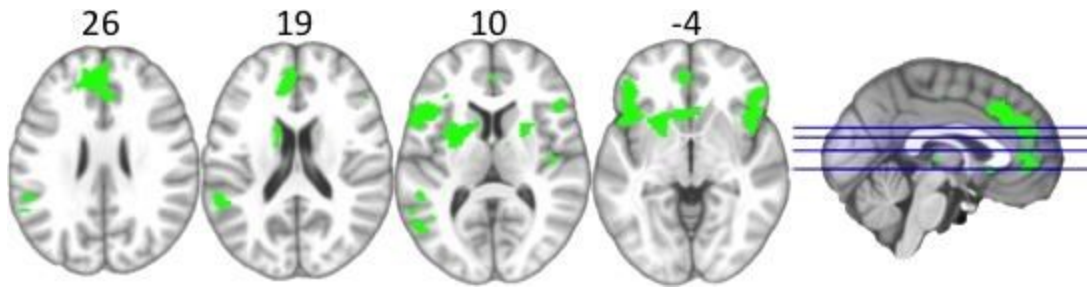


Figure 3.5. Most Significant Increases of V1 RSFC

In order to correlate the increases of V1 RSFC with subjective ratings and with alpha power, one z value was retrieved for all of the (significantly increased) regions. The significant areas with $p < 0.05$ were too widespread for this purpose, and therefore a threshold of $p < 0.01$ was used (5000 permutations) to define the most significant regions and subsequently derived the mean z value across all of these regions. A binarized mask of these regions is presented in this figure.

V1 RSFC	MNI_152 Coordinates						
	Volume(mm ³)	Difference; Max (z)	Placebo (z)	LSD (z)	x	y	z
Paracingulate/ACC	14912	4.95	1.13	5.85	47	85	48
Left Insula/IFG/Operculum	6992	4.72	1.55	4.75	62	77	26
Left Striatum/Subcallosal	5824	4.36	1.78	5.86	47	72	34
Left Supramarginal/Angular	5616	4.22	1.26	5.6	71	40	44
Right Insula/IFG/Operculum	5136	4.11	-0.93	3.72	23	69	35
MCC	2496	4.16	0.96	4.19	44	58	58
Right Supramarginal/Angular	2128	3.84	0.5	4.6	12	41	46
Right Lateral Occipital	2064	4.17	2.74	4.35	23	29	39
Right Striatum	2040	3.88	1.27	4.5	39	61	44
Posterior Thalamus	1296	4.76	3.22	6.42	47	52	38
Left Precuneus	1264	3.75	0.01	4.19	51	34	56
Left Frontal Pole	984	3.72	-0.26	3.92	58	92	48
Right Heschl's Gyrus	896	3.92	2.06	4.99	23	55	41
Cuneal	480	4.25	2.75	4.63	52	24	53
Left Precentral/NFG	400	3.46	1.55	5.04	71	67	55
Right Precuneus	360	3.82	-1.21	4.18	37	34	53
Left Planum Polare	344	3.48	0.19	3.6	66	52	35
Left Heschl's Gyrus	304	3.4	1.97	5.29	67	52	43
Right MFG	240	3.38	0.255	4.06	20	68	56
Right Putaman	224	3.98	0.21	4.11	33	63	34
Paracingulate	160	3.2	0.95	4.12	49	70	60
Right Putaman	160	3.28	1.93	5.05	35	70	34

Table 3.1. Coordinates of Increased V1 RSFC

Regions showing increased V1 RSFC ($p < 0.05$, cluster corrected) (Figure 3.1). All changes were in the direction of increased V1 RSFC under LSD. In order to get more segregated clusters, the cluster threshold was set to $z > 3$ (unlike in figure 3.1 in which $z > 2.3$). Furthermore, only clusters that were bigger than an arbitrary 20 voxels are reported. The placebo and LSD columns report the z value of each condition separately in the same point as Max.

ASC ratings		Experience of Unity	Spiritual Experience	Blissful State	Insightfulness	Disembodiment	Impaired Cognition	Anxiety	Complex Imagery	Elementary Imagery	Audio/Visual Synaesthesia	Altered Meaning	
Difference between correlations with V1-RSFC	Pearson r with Increased V1 RSFC	0.399	0.261	0.371	0.474	0.233	0.188	0.406	0.739	0.629	0.644	0.367	
	Difference between V1 RSFC-Complex Imagery correlation and correlations with other ASC items	Z	1.791	2.063	1.734	1.400	2.300	2.487	1.615		0.595	0.636	2.075
		p	*0.036	*0.019	*0.041	0.081	*0.010	*0.006	0.053		0.276	0.262	*0.019
	Difference between V1 RSFC-Elementary Imagery correlation and correlations with other ASC items	Z	0.750	0.992	0.840	0.553	1.505	1.624	0.938	-0.595		-0.075	0.851
		p	0.227	0.161	0.200	0.290	0.066	0.052	0.174	0.276		0.470	0.197
VAS ratings		Complex Hallucinations	Simple Hallucinations	Emotional Arousal	Positive Mood	Ego Dissolution							
Difference between correlations with V1-RSFC	Pearson r with Increased V1 RSFC	0.425	0.627	0.088	0.200	0.272							
	Difference between V1 RSFC-Simple Hallucinations correlation and correlations with other VAS items	Z	2.053		1.677	2.352	1.362						
		p	*0.020		*0.047	*0.009	0.087						

Table 3.2. Selectivity of Correlations with Subjective Ratings

Comparing correlations of imaging results with different ASC/VAS ratings. In this table, the hypothesis-driven significant correlations with visual dimensions of the experience, are compared with correlations of the same results with different ASC or VAS scales (for which no-strong prior hypotheses were held). The term “selectivity” is used to refer to a significant correlation being greater in strength than a (spurious) non-hypothesized correlation. The z values represent the difference between correlations. The z values were calculated using a web-utility (Lee and Preacher, 2013) that is based on the work of Steiger (1980). Correlations related to the visual system and visual experiences are bordered in red. If these correlations are indeed “selective” they will differ significantly from those that fall outside of their borders and indeed this is largely the case. It can be seen from the table that the following correlations are highly selective: V1 RSFC with complex imagery (ASC), and V1 RSFC with elementary hallucinations (VAS).

* $p < 0.05$, 1- tail.

3.4 Discussion

V1 showed increased RSFC to many cortical and subcortical regions. Furthermore increased V1 RSFC correlated with subjective ratings and with reduced alpha power measured in MEG. These results suggest that processing of eyes closed psychedelic imagery involves V1 and that communication patterns between V1 and the rest of the brain increase, suggesting that psychedelic imagery is a process that involves most of the brain together with V1, which relates to decreased segregation of networks as observed with psilocybin (Roseman, et al., 2014). This result has been replicated to some extent using previous psilocybin data acquired in the lab. Furthermore, this result has been replicated recently by a different lab using LSD as well (Supp. Figure 4 in appendix of Müller, et al. (2018)).

Results of V2 and V3 were similar to V1 but less pronounced. This might be due to the larger 5-HT_{2A} receptor density in V1 compared to V2 and V3 (Beliveau, et al., 2017; Watakabe, et al., 2008; Zilles, et al., 2002), or due to stronger connectivity patterns of V2 and V3 to the rest of the brain under placebo. This suggest, that V1, compared to V2 and V3, is more segregated from the rest of the brain at rest, and that the distinctiveness of the psychedelic effect is to reduce this segregation and increase the communication between V1 and the rest of the brain. Furthermore, reduced alpha power is the hallmark signal for visual processing, and therefore the significant correlation between V1 RSFC and reduced alpha power emphasis that the changes in connectivity patterns are related to visual processing. Important to note that this result does not necessarily lead to the source of the imagery, as it can be top-down to V1, bottom-up from V1, from another “low-level” source to V1, or all of the above. Still, this result strengthen the notion that to some extent V1 is processing psychedelic imagery in a similar way to information received from the eyes (de Araujo, et al., 2012).

In this analysis the focus was of specific visual regions as the hypothesis was related to the involvement of visual cortex. Yet, other larger scale approaches have been used to investigate both LSD and psilocybin. For example, on the same LSD dataset, an hypothesis-free analysis of global functional connectivity has been conducted and revealed that global functional connectivity of many high-level regions in the brain increased, and these increases were driven by larger functional connectivity to sensory areas including the middle visual network which corresponds to the primary visual cortex (Tagliazucchi, et al., 2016a). Furthermore, investigation of large scale RSNs has revealed a general increase in functional connectivity between networks (reduced segregation) both with LSD (Carhart-Harris, et al., 2016a) and psilocybin (Roseman, et al., 2014), but not with MDMA (Roseman, et al., 2014). These whole brain analysis have already revealed increased connectivity between visual regions and higher level regions, and these changes in connectivity patterns were related to a general increase in functional connectivity which is not specific to the visual cortex. Yet, this analysis, by focusing accurately on the primary visual cortex has revealed that the changes in connectivity of V1 are related to the subjective experience of psychedelic imagery. This suggest that global changes in connectivity patterns are related to different phenomenological aspects of the psychedelic experience based on the regions in which they occur. This pattern is also seen in regard to the subjective experience of ego-dissolution – while decreased *within* network connectivity is observed for all RSNs, only the decreases within the DMN relate to the subjective ratings of ego-dissolution (Carhart-Harris, et al., 2016a).

4. STUDY 2 |

Retinotopic Coordination

4.1 Introduction

Retinotopic organization means that nearby regions in the retina project to nearby cortical regions (Tootell, et al., 1988). Retinotopic mapping has helped in identifying the borders between neighboring visual regions (e.g. V1, V2, V3) (Serenio, et al., 1995). Furthermore, this technique can be used to identify within each of the visual regions subregions that correspond to different spatial locations (horizontal vs. vertical spatial specificity). Data obtained from retinotopic mapping can be valuable for understanding the visual system in resting state and can help us understand conditions characterized by abnormal visual experience such as visual hallucinations.

A similar paradigm to the one used in Nir, et al. (2006) was used in this chapter. This paradigm was modified into measuring RSFC changes between retinotopic subregions: Nir, et al. (2006) showed that at rest (closed eyes or open eyes with a fixation point) the visual system manifests slow widespread synchronized fluctuations. However, when a stimulus, e.g. a face or a building, was presented, the intrahemispheric connectivity between visual areas that correspond to the same stimuli (face-face or building-building) increased and the connectivity between different areas (face-building) decreased. They describe this as “spatial decoherence, i.e. the breakdown of overall synchrony into patterns of both strong and weak correlations between different functional regions, reflecting their functional specialization” (p. 1322). I have theorized that under LSD-induced closed-eyes psychedelic imagery, retinotopic subregions of the visual cortex would show a similar

pattern of changes: RSFC between subregions with similar retinotopic representation will be stronger than RSFC of subregions with different retinotopic representation.

The hypothesis that at rest, ‘spontaneous’ functional connectivity between visual areas is according to retinotopic organization has been tested in a number of studies which suggested that to some extent that is the case (Gravel, et al., 2014; Heinzle, et al., 2011; Raemaekers, et al., 2014), a result which has been seen with congenital blind subjects as well (Bock, et al., 2015; Butt, et al., 2015; Striem-Amit, et al., 2015). However, Raemaekers, et al. (2014) suggested that these fine-scaled connectivity patterns can be masked by large-scale networks. The reason to hypothesize that under LSD these retinotopic correlations would be higher is that psychedelic visual hallucinations do not always encompass the whole view field, and sometimes the hallucination has a certain location in space and therefore, likely, a certain retinotopic location in the brain. To test this idea we chose the subregions of V1 and V3 that correspond to the vertical and horizontal orientation. I have predicted that RSFC between retinotopically-organized patches of V1 and V3 that possess congruent retinotopic specificity (i.e. V1 horizontal - V3 horizontal meridian or V1 vertical - V3 vertical meridian) would be greater than RSFC between incongruent patches (e.g. V1 horizontal – V3 vertical) under LSD, and less under placebo. That is, the impact of LSD on spontaneous activity within retinotopically organized patches of V1 and V3 would be consistent with what one would expect from visual stimulation (Nir, et al., 2006). The reason that this analysis was not conducted for V1-V2 and V2-V3 is that such analysis could be confounded by the anatomical proximity of the representations of the vertical and horizontal meridians respectively. The retinotopic representations of neighboring regions are mirroring each other – V1 retinotopy is from horizontal to vertical while V2 retinotopy is from vertical to horizontal (the vertical meridian is the border between V1 and V2, which means that the connectivity between V1 vertical and V2 vertical can be high just due to their spatial proximity). In order to avoid a distance-dependent confound, the analysis was

conducted on V1-V3 only which have a parallel retinotopic organization (horizontal to vertical).

4.2 Methods

BOLD Pre-processing

The pre-processing here was similar to the preprocessing that is presented in chapter 2, except that all analyses were done in native space without registration to MNI space. Furthermore, four more subjects were discarded due to imperfect identification of horizontal and vertical meridian retinotopic patches of V3. Overall, 10 subjects were used in this analysis.

V1-V3 retinotopic coordination

V1 and V3 were subdivided using the vertical versus horizontal meridian activations to yield four patches ($V1_{hor}$, $V1_{ver}$, $V3_{hor}$, $V3_{ver}$). After horizontal and vertical retinotopic patches of V1 and V3 were identified using the retinotopic localizer described above (horizontal/vertical patches of V1 and V3 are regions which were activated from a horizontal/vertical stimuli and are processing visual information in the horizontal/vertical field of view), the mean BOLD time-series for $V1_{hor}$, $V1_{ver}$, $V3_{hor}$, $V3_{ver}$ (hor = horizontal orientation, ver = vertical orientation) were derived from each of the LSD and placebo resting-state scans in native space. The results below were averaged across the two resting-state scans (both placebo and LSD had two resting-state scans within each session). Parameter estimates (β) of linear regression were calculated between $V1_{hor}$ - $V3_{hor}$ (β_{hor_hor}), $V1_{hor}$ - $V3_{ver}$ (β_{hor_ver}), $V1_{ver}$ - $V3_{hor}$ (β_{ver_hor}), $V1_{ver}$ - $V3_{ver}$ (β_{ver_ver}). These β values represent RSFC between two retinotopic patches. Regression was used rather than correlation coefficients because differences between Pearson's correlations could be a result of either signal or noise differences; therefore, it is preferable to perform regression and look for drug-placebo differences on the β

values (Friston, 2011). Retinotopic coordination was calculated as follows (Figure 4.3A):

$$\text{retinotopic coordination} = (\beta_{\text{hor_hor}} + \beta_{\text{ver_ver}} - \beta_{\text{hor_ver}} - \beta_{\text{ver_hor}}) / 2$$

4.3 Results

Subjective ratings

The mean±SD between-condition difference in within-scanner VAS ratings of visual hallucinations/imagery were 9.73±6.43 and 7.37±6.87 for simple and complex imagery, respectively (range = 0-20). The mean difference in the retrospective ratings of visual imagery were 65±34 and 42±28 for elementary and complex imagery, respectively (range = 0-100), $p < 0.05$ (Bonferonni corrected) for all of the above changes in subjective ratings.

Retinotopic localizer

Retinotopic patches ($V1_{\text{hor}}$, $V1_{\text{ver}}$, $V3_{\text{hor}}$, $V3_{\text{ver}}$) of the 10 subjects, and their surface areas (mm^2), are presented in Figure 4.1. This figure illustrates that retinotopic regions vary in size and location across subjects and emphasis the advantage of retinotopic mapping over an atlas. For illustration purposes, the surface average of the retinotopic activation is presented in Figure 4.2. The average was calculated by sampling each subject's morphed sphere onto the canonical icosahedral sphere surface (1 smoothing step; nearest neighbour, forward and reverse). The averaged sphere was sampled onto Freesurfer's average surface.

V1-V3 retinotopic coordination

Mean values across subjects for retinotopic coordination (i.e. the difference in RSFC between retinotopically congruent patches and incongruent patches) were significantly greater ($t = 3.93$, $p = 0.0018$, 1-tail, paired t-test, Cohen's $d = 1.6$) under LSD (0.068 ± 0.058) than under placebo (-0.005 ± 0.02) (boxplot is presented in Figure 4.3B). Retinotopic coordination for each subject and for each condition, are shown in Figure 4.3C (9 of 10 subjects showed a change in the predicted direction). This result is based on the mean of the two resting-state scans (both the placebo and the LSD session contained two resting-state scans) but it was also significant for each of the resting-state scans alone ($p = 0.0288$ and $p = 0.0057$). Furthermore, the results showed the same trend for the right and left hemispheres separately ($p = 0.022$ and $p = 0.078$, respectively) and the result was also significant when using Pearson's correlation coefficient instead of regression to calculate RSFC ($p = 0.033$). Importantly, the increased retinotopic coordination across subjects did not correlate with increased head motion under LSD compared with placebo ($r = -0.83$, $p = 0.999$, 1-tail) – the correlation is negative which means that head motion did not confound the dataset by artificially *increasing* retinotopic coordination, and the opposite might be the case – that head motion might have masked some increases in retinotopic coordination in subjects that had high head movement. Retinotopic coordination did not correlate with rating scales of psychedelic imagery (e.g Elementary & Complex Imagery factors of ASC, or VAS ratings of Simple & Complex Hallucinations).

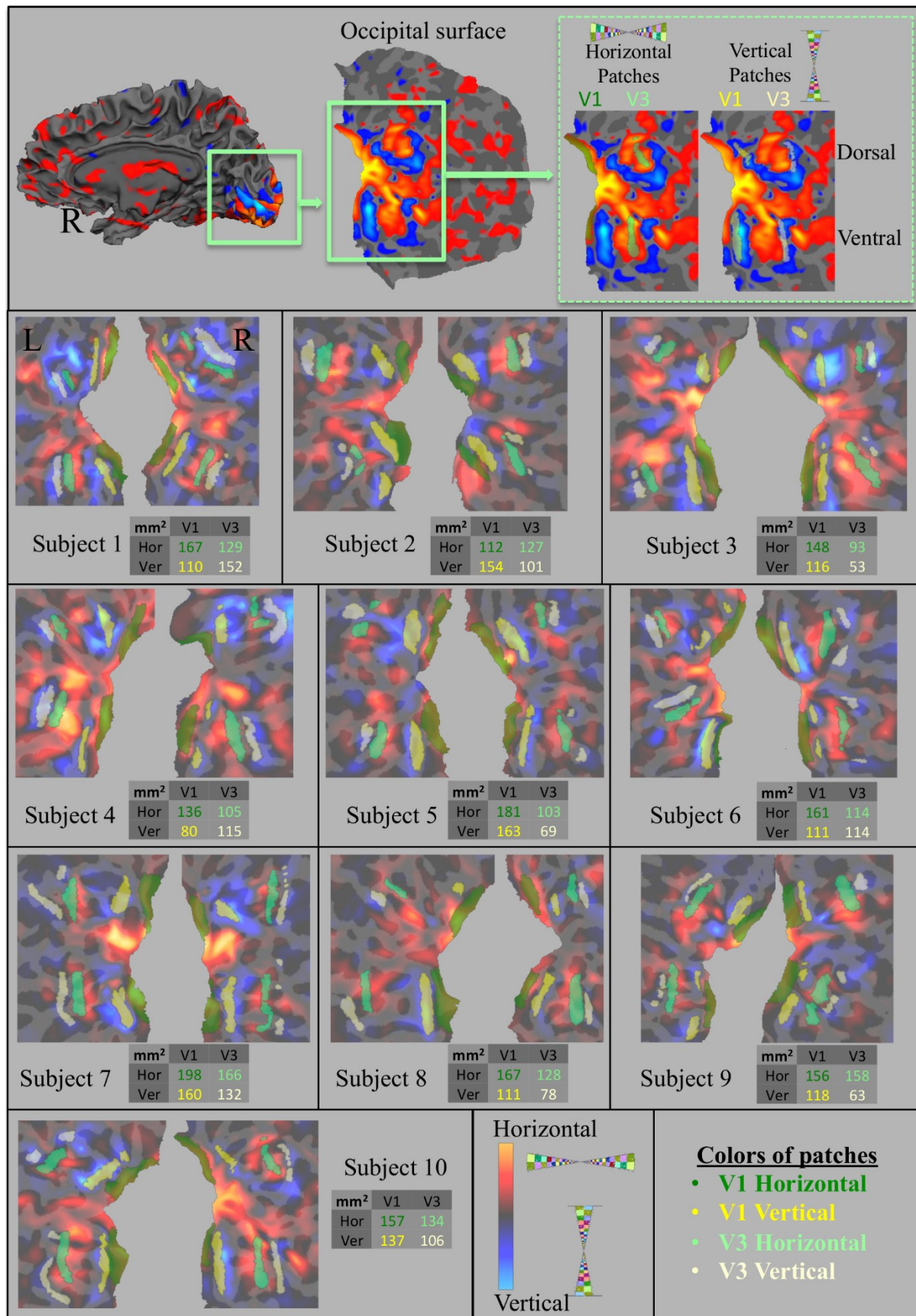


Figure 4.1. Retinotopic patches of all subjects

Activity based on retinotopic localizer is projected onto the occipital surface of each subject. Hot and cold colors represent horizontal and vertical meridian activations, respectively. The top panel is the right hemisphere of an illustrative subject. Below, horizontal (green) and vertical (yellow) patches were identified for each subject in both V1 and V3. For each subject, the surface areas (mm^2) of these patches are displayed in a table.

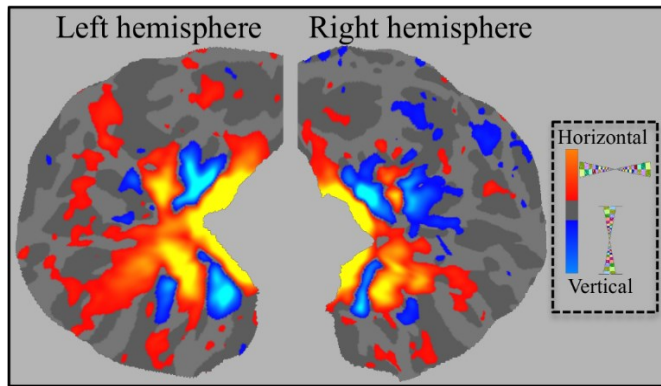


Figure 4.2. Average of retinotopic activation across subjects

Average retinotopic activation of 10 subjects is projected onto the Freesurfer average occipital surface. Hot and cold colors represent horizontal and vertical meridian activations, respectively.

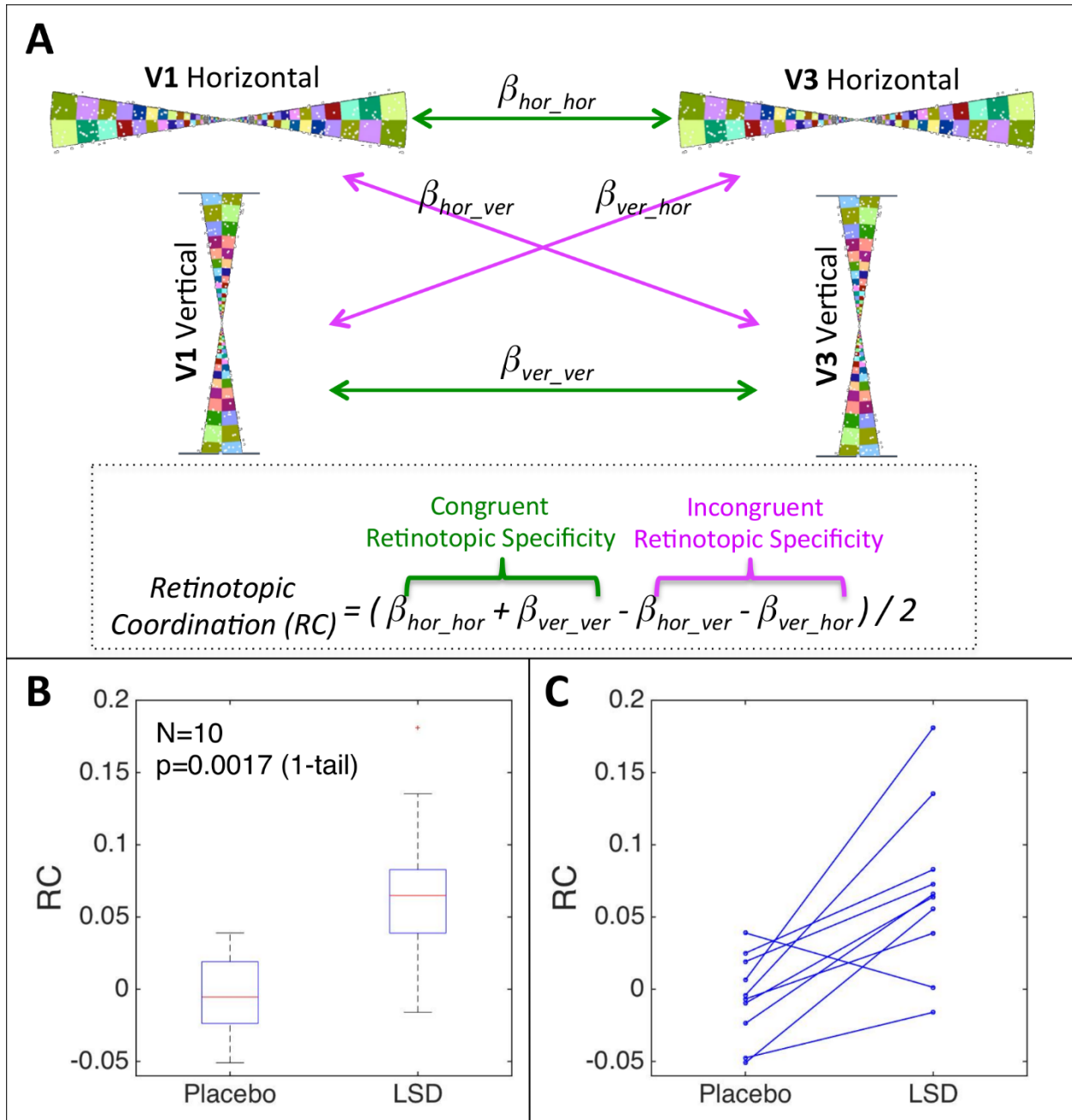


Figure 4.3. Increased retinotopic coordination (RC) under LSD

A) Calculating RC for each subject for each condition. Horizontal and vertical patches of V1 and V3 were identified using a retinotopic localizer (the wedges in this figure are taken from the video). Four regressions between patches of V1 and V3 produced four regression coefficients (β values) that represent the strength of RSFC. RC was calculated by adding the RSFC (β) values of patches with the congruent retinotopic

specificity and then subtracting the RSFC β values of patches with incongruent retinotopic specificity. B) Boxplot of RC for Placebo and LSD. C) RC for all 10 subjects for Placebo and LSD.

4.4 Discussion

The present study found that LSD-modulated-RSFC within the visual cortex reflects the intrinsic retinotopic architecture of the brain; i.e. RSFC between patches of V1 and V3 that possess a congruent retinotopic representation was stronger than RSFC between patches possessing incongruent retinotopic representations. Consistent with the previous chapter and other studies (de Araujo, et al., 2012), these findings suggest that the primary visual cortex is involved in the processing of eyes-closed psychedelic imagery.

The increased retinotopic coordination between V1 and V3 under LSD did not correlate with ratings of visual hallucinations. One possible explanation for this is that increased retinotopic coordination reflects a specific alteration in the spatial properties of psychedelic imagery and not its general intensity. For example, while the overall intensity of the hallucinatory experience may increase (e.g. with a higher dose of LSD) the psychedelic imagery may lose some of its spatial properties and this might be not expressed as an increase in retinotopic coordination. This matter could be addressed by including a different measure of the hallucinatory experience that enquires specifically about the spatial acuity of the psychedelic imagery, as well as its location in space. We would predict that psychedelic visions that are especially sharp or vivid and clearly located in space would relate to an increase in retinotopic coordination. Another possible explanation for the lack of correlation between the subjective intensity of the psychedelic imagery and the reported RSFC results is that higher levels of motion interfered with accurate measurements of retinotopic

coordination: indeed, subjects that had higher differences (LSD-placebo) in head motion had a lower difference in retinotopic coordination, i.e. head motion “diluted” the main drug effect on retinotopic coordination.

Another possible explanation of our main finding is that the retinotopic coordination observed under LSD was an epiphenomenon of a more general increase in “activity” within the relevant brain regions. Other results from the same LSD dataset do suggest that there are changes in activity within visual areas that might be construed as consistent with increased “activity”: e.g. increased CBF and decreased MEG alpha power (Carhart-Harris, et al., 2016a). However, these effects did not correlate with the increased retinotopic coordination observed here ($p = 0.98$, $p = 0.97$, 1-tail, respectively) and therefore cannot be used to explain this study’s main findings.

Other studies that used measures similar to retinotopic coordination, in resting state, have found that at rest subregions of the visual cortex are functionally connected in a retinotopic manner (Bock, et al., 2015; Butt, et al., 2015; Gravel, et al., 2014; Heinzle, et al., 2011; Raemaekers, et al., 2014; Striem-Amit, et al., 2015). In our analysis we did not find retinotopic coordination under placebo. The discrepancy might be related to the suggestion raised by Raemaekers, et al. (2014) that the fine-scaled connectivity patterns are seen only after regressing out large scale resting state networks or regressing out the global signal. From the same LSD data set it has been shown that the variance of RSNs is reduced under LSD (Carhart-Harris, et al., 2016a). This change might explain why retinotopic coordination is increased - as the large scale resting state signal is decreased and therefore masks less of the fine-scaled retinotopic connectivity. Another explanation for this discrepancy, is that in this analysis a relatively crude measure of retinotopic localization was used for time efficacy, while the above studies have used longer and more accurate scans for

retinotopic localization and therefore were successful in identifying these patterns in normal resting state.

A further limitation of this study is the sample size ($N = 10$). Unfortunately, psychedelic neuroimaging studies are sensitive to data loss issues, mainly related to high levels of head motion associated with the drug condition. Future studies should take this into account and collect more data than would ordinarily be needed in order to compensate for potential data loss. Even after correcting for motion, however, we had a very clear prior hypothesis that proved correct in 9 out of the 10 subjects and post-hoc analyses indicated that head motion had a deleterious rather than a contributory influence on this predicted effect. Ideally, in order to show that retinotopic coordination is related to visual processing, we could have acquired fMRI scans while our subjects watched a movie and then measured retinotopic coordination in this condition.

5. STUDY 3 |

Dynamics

5.1 Introduction

The visionary elements of the psychedelic experience are known to progress from elementary imagery to complex imagery (see more in Background 1.6.4 and 1.6.5) (Klüver, 1928; Knauer and Maloney, 1913; Lewis-Williams, 2002; Meyer, 1994; Reichel-Dolmatoff, 1975; Shanon, 2002b). It is possible to measure the dynamics of the experience through the dynamics of neural activity, especially for short acting psychedelic like DMT (Timmermann, et al., 2018), or psilocybin IV (Carhart-Harris, et al., 2011). In the Background section, I have suggested that 1) the progression of psychedelic imagery (1.6.5) is related to visual cortex hierarchy (1.9.1); and 2) that the magnocellular (dorsal, “where”) visual pathway is more involved in processing simple visual imagery and it precedes the parvocellular (ventral, “what”) pathway which is more involved in processing complex visual imagery (1.9.8). In this chapter, this hypothesis is tested by observing the dynamics of the onset or “come-up” of the experience with psilocybin IV, which has fast phenomenological dynamics (Carhart-Harris, et al., 2011). This was done by plotting the BOLD time course of different subregions within the visual cortex and observing whether the changes in BOLD activity are ordered by the cortical visual hierarchy or by dorsal and ventral visual pathways.

Furthermore, to investigate the similarity, between subjects, of neural activity dynamics, Inter-Subject Correlation (ISC) was used for whole brain analysis in an exploratory manner (Hasson, et al., 2004). It has been shown with this method that

subjects that watch the same movie also share the same dynamics of brain activity. In this method, voxel to voxel correlation between a pair of subjects is calculated, which result in a correlation map between the temporal activity of two subjects (while watching a movie, regions with similar dynamics will show high correlations, and therefore it can be concluded that these regions are involved in watching the movie). This analysis is conducted on possible pairs of subjects within the group, and an average is calculated across all pairs. After identifying regions with high ISC, the mean BOLD time course of these regions is plotted to reveal moments of shared high activity (e.g. Fusiform Face Area (FFA), will show high ISC while watching a movie, and the mean time course across subjects of the FFA will correspond to moments in the movie in which faces appear). In case the onset-phase of psilocybin IV has similar dynamics across subjects, then high ISC will be observed.

It was hypothesized that with psilocybin IV, visual areas will show high ISC which corresponds to the onset-phase of drug effects. Furthermore, it was hypothesized that for magnocellular visual regions BOLD time course will gradually increase from injection, before an increase of parvocellular regions, and that a gradual increase in activity of different subregions of the visual cortex will occur in the order of the visual hierarchy, i.e. V1 first followed by V2 etc.

5.2 Methods

fMRI Preprocessing

Psilocybin data was preprocessed as detailed in the main Methods section except for the following: 1) Highpass filter was not applied; 2) Detrending was not applied; and 3) Head motion time course derivatives were used as nuisance regressors instead of head motion time courses. The reason for changing these preprocessing steps was that, for this analysis, the signal of interest is of low frequency (i.e. the onset of drug

effects) and these preprocessing steps could therefore obstruct the signal of interest. The length of the BOLD data that was used was 2 minutes and 51 seconds – from 9 seconds after the beginning of psilocybin IV infusion until 2 minutes after the infusion (Infusion time was 60 seconds; first 3 TRs after infusion were taken out of the analysis).

Visual Hierarchy

Different regions of the visual cortex hierarchy were identified for each subject in inflated native space, based on Wang's visual topography atlas (Wang, et al., 2014) from the following link: https://hub.docker.com/r/nben/occipital_atlas/. Regions of the ventral stream were V1v, V2v, V3v, hV4, VO1, VO2, PHC1, and PHC2. Regions of the dorsal stream were V1d, V2d, V3d, V3a, IPS0, IPS1, IPS2, and IPS3 (Figure 5.1). BOLD time courses of each of the ROI for each subject were standardized and temporally smoothed with a span of 5 TRs (Matlab) to account for inter-subject temporal variation. Average time courses were calculated across subjects.

To show whether the dynamic patterns are significant a Generalized Linear Model was calculated with z value (the y axis in figure X) as the dependant variable, subject (N=9) and time point (N=57) as factors, and ROI as covariate (in which the 8 regions of the visual hierarchy are numbered from 1 to 8). The model included a main effect of time and an interaction of Time*ROI. A significant interaction will suggest that there is an order of z values based on the ROI hierarchy and this changes in Time. To inform whether the difference between psilocybin and placebo was significant, another model was calculated with condition (psilocybin or placebo) as another factor, and the interaction of interested was Time*ROI*Condition

Ventral vs. Dorsal Activity

Based on the above atlas (Wang, et al., 2014), five high level regions were identified as ventral stream (hV4, VO1, VO2, PHC and PHC21), and five high level regions were identified as dorsal stream (V3a, IPS0, IPS1, IPS2, and IPS3). Time courses of each of both streams were standardized and temporally smoothed with a span of 5 TRs. Average time courses were calculated across subjects.

Inter-Subject Synchronization (ISC)

A whole brain ISC exploratory analysis was conducted. This analysis was conducted to measure similar dynamics across subjects in a hypothesis free manner – without any regressor of interest. BOLD data of all subjects was demeaned in order to make datasets comparable across subjects. Pearson correlation followed by Fisher transformation were calculated between all pairs of subjects, resulting in whole brain ISC maps between all possible pairs of subjects (36 possible pairs for 9 subjects) – each of these whole brain maps shows for each voxel the correlation coefficient of the two BOLD signals of the pair of subjects. The significance of ISC of the psilocybin condition across pairs was calculated with nonparametric test using FSL randomize (Winkler, et al., 2014) (5000 permutations and Threshold Free Cluster Enhancement (TFCE)). The significant areas were compared to placebo with FSL randomize in a within subjects design. BOLD time courses of the significant ROIs that resulted in the ISC analysis were extracted for each subject, standardized and temporally smoothed with a span of 5 TRs to account for inter-subject variation, and an average time course across all subjects was calculated for each of these ROIs to inspect the dynamics of interest for each ROI.

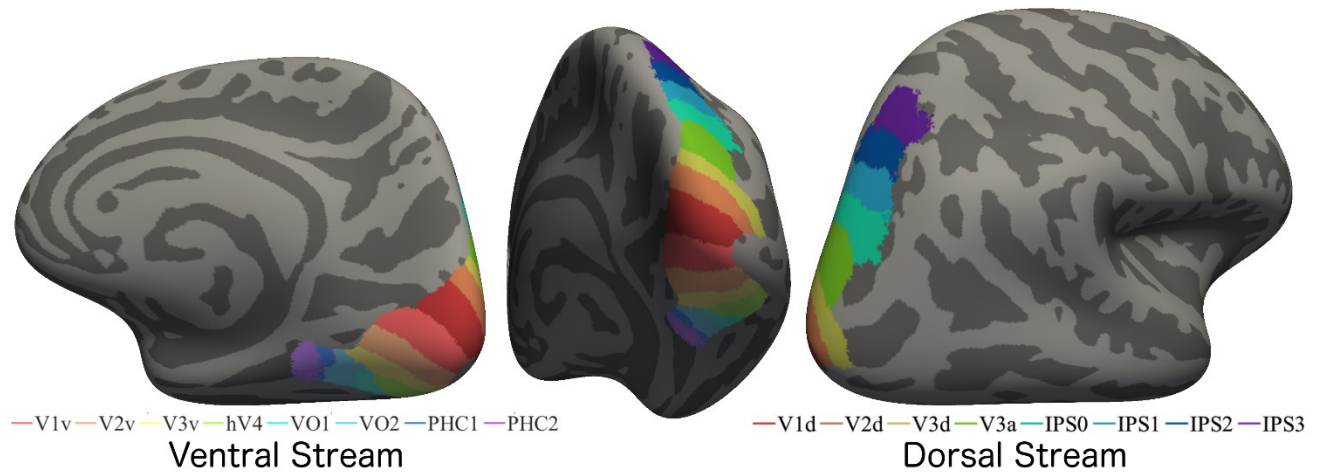


Figure 5.1. ROIs of Ventral and Dorsal Streams

ROIs of ventral (light colors) and dorsal (dark colors) streams are presented on fsaverage inflated cortical surface. ROIs are chosen from an atlas by Wang, et al. (2014), and were localized for each subject in native space. Regions of the ventral stream are V1v, V2v, V3v, hV4, VO1, VO2, PHC1, and PHC2. Regions of the dorsal stream are V1d, V2d, V3d, V3a, IPS0, IPS1.

5.3 Results

Visual Hierarchy

Average time courses, across subjects, of subregions of the ventral and dorsal streams were plotted (Figure 5.2). Visual inspection of the plots suggest that the dynamics of the onset phase of the ventral stream are order by region (red to purple in Figure 5.2). To show whether the dynamic patterns are significant a Generalized Linear Model was calculated with z value (the y axis in figure X) as the dependant variable, subject (N=9) and time point (N=57) as factors, and ROI as covariate (in which the 8 regions of the visual hierarchy are numbered from 1 to 8). The model included a main effect of time and an interaction of Time*ROI. A significant interaction will suggest that there is an order of z values based on the ROI hierarchy and this changes in Time. To inform whether the difference between psilocybin and placebo was significant, another model was calculated with condition (psilocybin or placebo) as another factor, and the interaction of interested was Time*ROI*Condition

Ventral vs. Dorsal Activity

Average time courses, across subjects, of high-level ventral and dorsal streams were plotted (Figure 5.3). Visual inspection of the plots revealed no difference in temporal dynamics between ventral and dorsal streams. Furthermore, visual inspection of time courses of each subject separately revealed no difference. However, both high-level areas of ventral and dorsal stream showed an initial decrease in activity (until ~50s from injection) and then a gradual increase (until ~100s from beginning of infusion). Furthermore, this was observed for all subjects inspected separately.

Inter-Subject Synchronization (ISC)

ISC was significant ($p < 0.05$, 5000 permutations, TFCE) within the right inferior temporal gyrus (Figure 5.4, top), however, two more clusters were found within the CSF which are probably of non-neural origin (near superior draining vein and 3rd ventricle). The average time courses, across subjects, of these three clusters increase gradually from the beginning of the infusion until 30 seconds into the infusion (this increase is observed for all subjects separately). As the time course of the two CSF clusters increase in a similar way to the time course of inferior temporal gyrus, it is better not to conclude any neural origin for the ISC of inferior temporal gyrus. This also puts into doubt the validity of the results of ventral and dorsal stream (Figure 5.3) as they follow an opposite pattern to that of CSF clusters, suggesting that they might be of non-neural origin as well. In a further exploratory analysis, ISC without randomization and without cluster correction (TFCE) and with a threshold of $Z > 3.1$, revealed another cluster in the right anterior parahippocampal gyrus (MNI coordinates: 18 -1 -29, max z value = 8.35). However, this cluster timecourse had similar dynamics to the two CSF clusters as well, and therefore no conclusions were drawn based on this result.

To further investigate ISC without the potentially noise components, the psilocybin data was preprocessing again, with an addition of the two time courses of the CSF clusters as nuisance regressors. After regressing out these components the ISC analysis was repeated (Figure 5.5). ISC was significant ($p < 0.05$, 5000 permutations, TFCE) within right inferior temporal gyrus, right parahippocampus, left supramarginal gyrus, and bilateral precuneus. An initial increase in BOLD immediately after injection was observed for the right inferior temporal gyrus, and an initial decrease was observed for the other three regions.

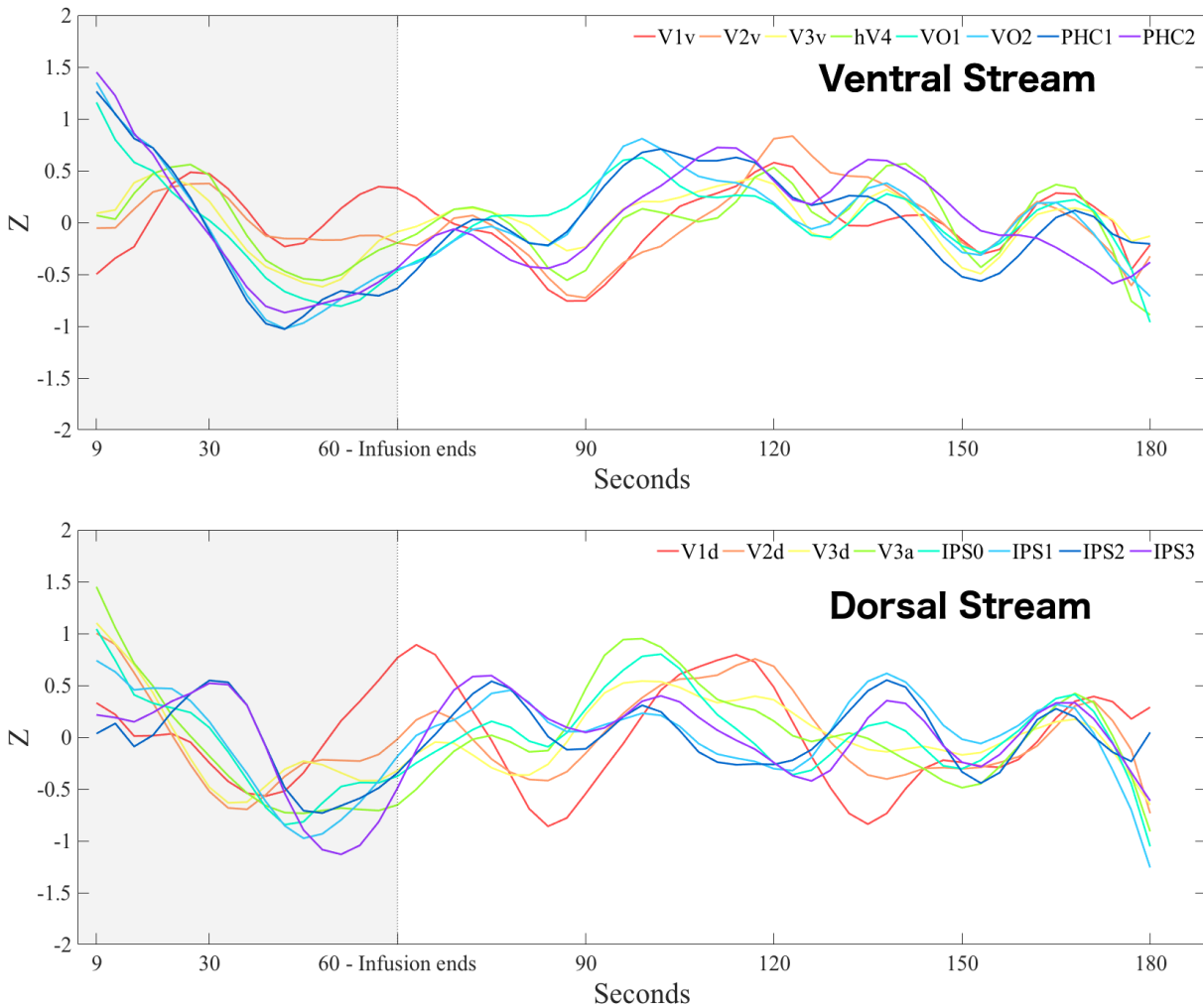


Figure 5.2. Visual Hierarchy BOLD Time Courses

Average time courses of different regions of the ventral and dorsal streams are presented. The order “up-stream” of ventral regions is V1v, V2v, V3v, hV4, VO1, VO2, PHC1, and PHC2. The order of dorsal stream is V1d, V2d, V3d, V3a, IPS0, IPS1, IPS2, and IPS3. Visual inspection of time courses reveal no difference in temporal dynamics. Infusion lasted for 60 seconds (grey area). However, do notice that during the beginning of the onset phase (injection time), in the ventral stream, there is an initial decrease in high level regions and a no change in low level regions.

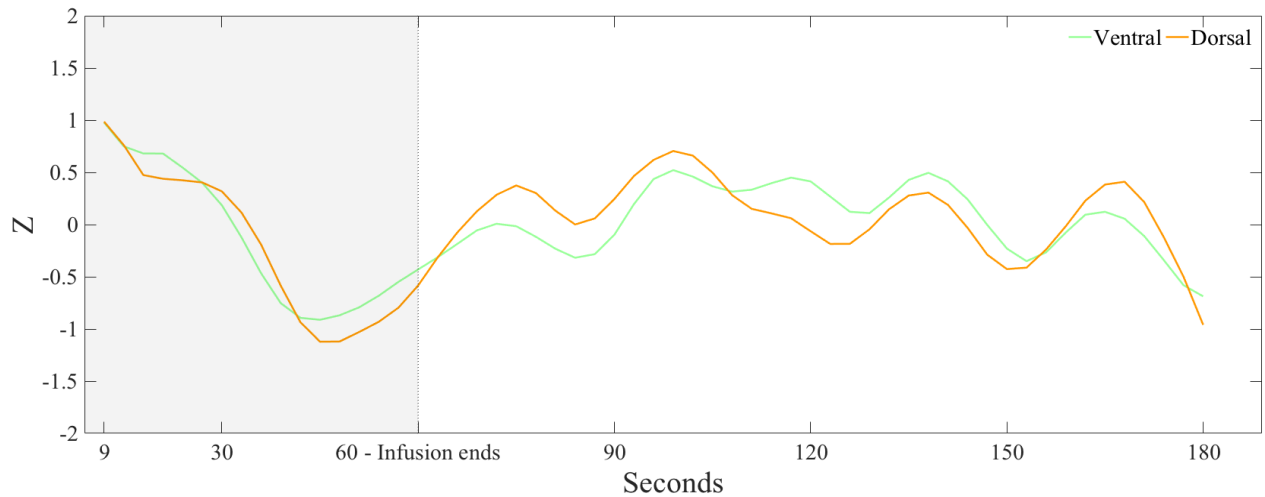


Figure 5.3. Ventral vs. Dorsal BOLD Time Courses

Average time courses, across subjects, of different high-level ventral and dorsal streams are presented. The ventral stream was conceived from hV4, VO1, VO2, PHC1, and PHC2. The dorsal stream was conceived of V3a, IPS0, IPS1, IPS2, and IPS3. Visual inspection of time courses reveal no difference in temporal dynamics. Infusion lasted for 60 seconds (grey area). Both ventral and dorsal streams showed an initial decrease which was followed by a subsequent increase, a dynamic that was observed for all subjects separately as well.

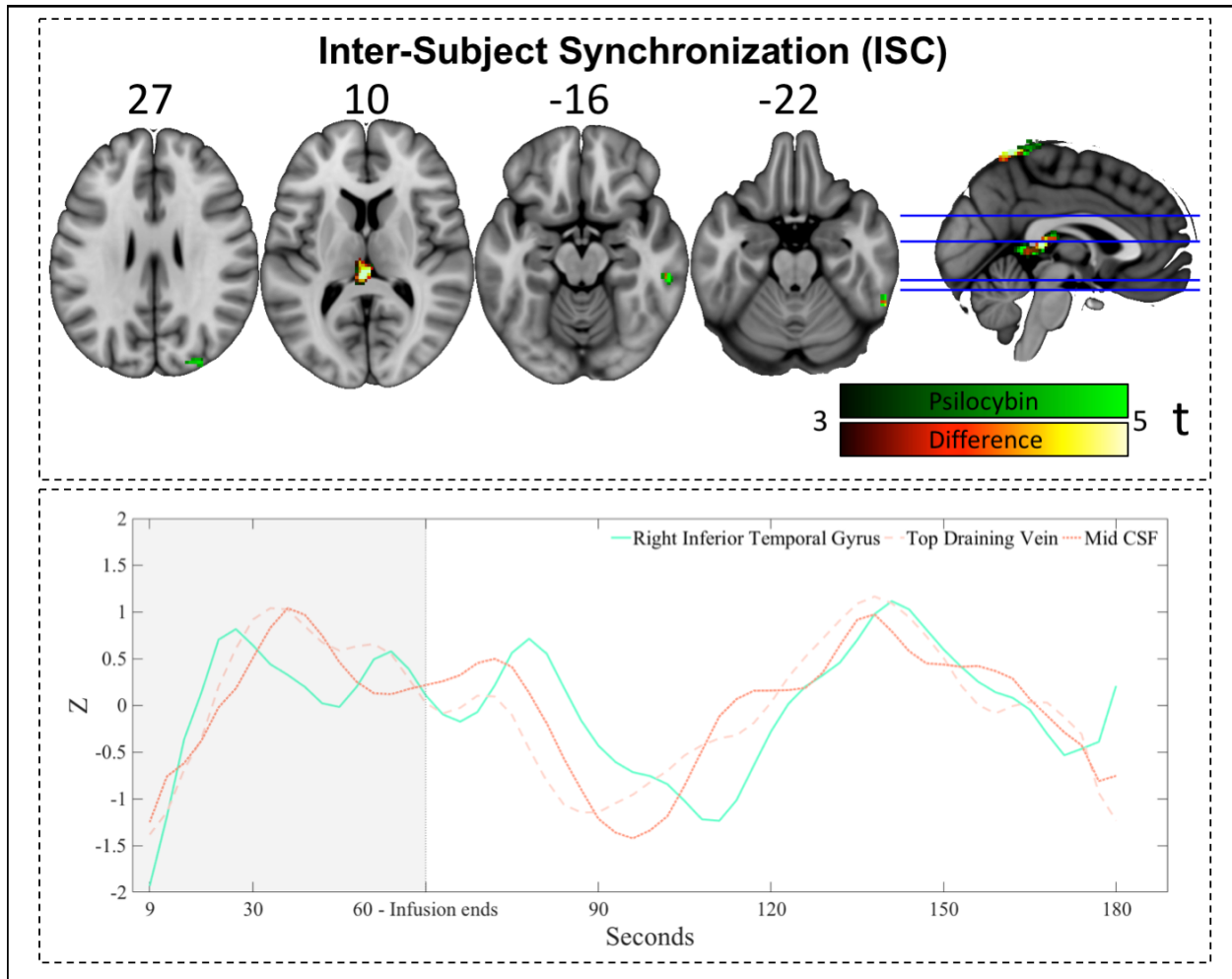


Figure 5.4. Inter-Subject Synchronization

Top: ISC t values are presented for psilocybin (green color) and for psilocybin>placebo (hot color). One cluster of interest was found in right inferior temporal gyrus (z slices -16 and 22). Another cluster in the right lateral occipital cortex was significant for psilocybin but not for the difference between psilocybin and placebo (z slice 27). Furthermore, two significant clusters were found in CSF (near superior draining vein and 3rd ventricle), which are probably due to the dynamics of physiological changes (heart rate and breathing patterns). Infusion lasted for 60 seconds (grey area). $P < 0.05$ (5000 permutations, TFCE).

Bottom: Average standardized time courses (across subjects) are presented for the significant regions from the top. The time course of the cluster in the right temporal

inferior gyrus increases gradually during the beginning of the infusion, an increase that was observed for all subjects separately. However, the time courses of clusters located in CSF (top draining vein, and 3rd ventricle) also increase during the beginning of the infusion. As the patterns of increases are similar, it is possible that the increase within inferior temporal gyrus is due to non-neural origin (e.g. heart rate, breathing).

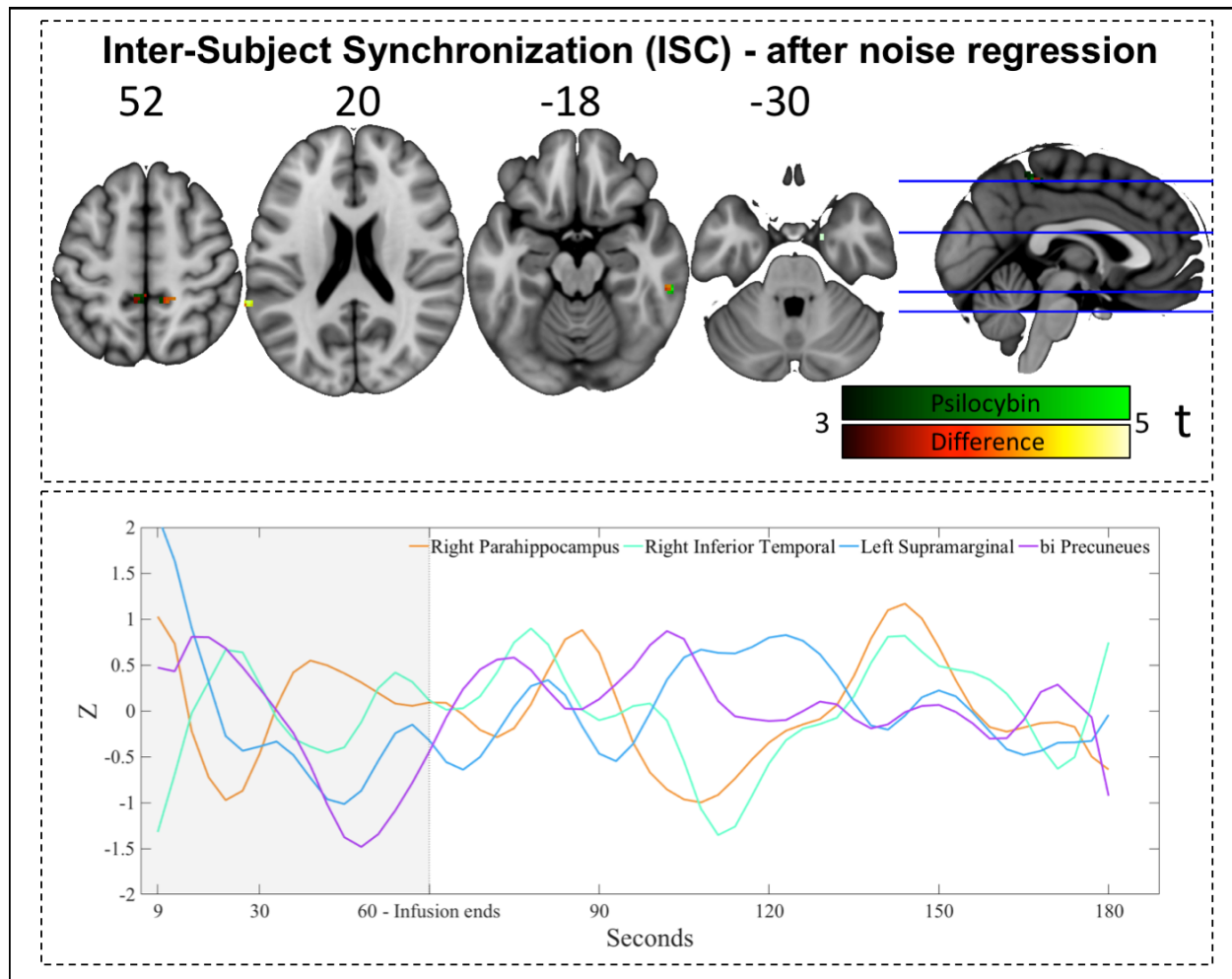


Figure 5.5. Inter-Subject Synchronization – after noise regression

ISC analysis has revealed two CSF components which are probably due to a non-neural source (Figure 5.4). Therefore, the same ISC analysis was repeated after regressing out these two CSF regions.

Top: ISC t values are presented for psilocybin (green color) and for psilocybin>placebo (hot color). Four clusters of interest were found: right parahippocampus ($z = -30$), right inferior temporal gyrus ($z = -18$), left supramarginal gyrus ($z = 20$), and bilateral precuneus ($z = 52$). $p < 0.05$ (5000 permutations, TFCE).

Bottom: Average standardized time courses (across subjects) are presented for the significant regions from the top. An initial decrease was observed for right parahippocampus, precuneus, and left supramarginal. An initial increase was

observed for right inferior temporal. A separate inspection of all 9 subjects has revealed that most of the subjects had similar dynamics for these regions immediately after injection.

5.4 Discussion

In this chapter the BOLD dynamics that might relate to the dynamics of psychedelic imagery have been explored. It has been hypothesized that activity will increase in the order of the visual cortex hierarchy and it was hypothesized that activity will increase first in the dorsal stream and then in the ventral stream. Furthermore, a whole brain exploratory ISC analysis has been conducted to reveal other similarities in the dynamics of the onset-phase of the drug experience. Only one result in this chapter was significant and that was increased ISC in right inferior temporal gyrus (Figure 5.4, top). However, increased ISC has been observed in the CSF as well (near superior draining vein and 3rd ventricle) and the dynamics of CSF BOLD signal were similar to the dynamics of right inferior temporal gyrus (Figure 5.4, bottom). Therefore, this result is not discussed further as it is probable that it has non-neural origins. Yet, ISC was repeated after regressing out the two CSF components and revealed 4 significant clusters. Three of these cluster showed an initial decrease during injection time – right parahippocampus, precuneues, and left supramarginal – and one cluster – in the inferior temporal gyrus - showed and initial increase.

Some interesting patterns have been found during the 60 seconds of injection time which was the very initial onset phase. As mentioned, ISC revealed a decrease in a number of clusters during this phase and an increase in the inferior temporal gyrus. Furthermore, within the parvocellular (ventral) visual stream, initial decreases have been observed in higher level visual areas compared to lower level ones (Figure 5.2). As the beginning of the onset phase is characterized with more simple imagery than complex imagery (Shanon, 2002a) – this might be associated with an initial deactivation of high level modalities compared to lower level ones. This hypothesis will be further tested in future research.

In the introduction of this thesis I have suggested that the parvocellular (dorsal) stream is more involved in simple imagery, and that the magnocellular (ventral)

stream is more involved in complex imagery. Furthermore, simple imagery tends to precede complex imagery, which led me to suggest that the dorsal stream will be activated before the ventral stream. This was not observed in this study but it will be tested again in future studies with better designs which explore more accurately the phenomenological dynamics of the experience, as in Timmermann, et al. (2018). Better temporal mapping of the subjective experience, using methods such as microphenomenology (Petitmengin, 2006), will allow to have more accurate predictions of the neural signal that is related to each of these phenomenological dynamics. This will help differentiating the neural correlates of each of the subjective experiences associated with psychedelics.

6. DISCUSSION

“Connecting
I am connecting
I am doing it with great joy
The icaros connect with me
I am singing

With this strong connection
I am purifying your bodies
Now, I bring good visions
The spirits of the plants are arriving”

— Olivia Arevalo

[Icaro](#)

This thesis focused on neural correlates of psychedelic imagery. Other studies in the past have showed that the visual cortex is activated with eyes closed under the influence of psychedelics, as measured with fMRI (Carhart-Harris, et al., 2012c; de Araujo, et al., 2012), or as shown as alpha power suppression in many human and animal studies (see section 1.8.4). Instead of focusing on activity, this thesis was focused on different elements of connectivity of the visual system and of the dynamics of the visual system.

In chapter 3, it was found that, under LSD, V1 showed increased functional connectivity with many regions in the brain and that this increase correlated with the subjective strength of psychedelic imagery and with alpha power suppression. These results suggest that the many cortical regions, together with V1 are involved in processing psychedelic imagery. Furthermore, alpha power suppression is the most reliable neural correlate of the psychedelic experience, and a reliable marker for any visual experience. The correlation between V1 RSFC and alpha power suppression strengthen the reliability of this result, its neural origin, and emphasize that changes in connectivity relate to visual processing.

In chapter 4, it was found that RSFC between V1 and V3 was dependent on their retinotopic architecture, meaning that, under LSD, RSFC was larger in regions of V1 and V3 with congruent retinotopic architecture, than with incongruent retinotopic architecture. Retinotopic architecture is the representation in the brain of the visual input from the eyes – areas of the visual field (the world that we look at) that are spatially near each other will also be near each other in the cortex. Increased retinotopic coordination under LSD, with eyes closed, suggest that the visual cortex is processing eyes closed psychedelic imagery as if it was spatially localized in the visual field. This finding is consistent with the idea that eyes-closed psychedelic

imagery under LSD are underpinned by brain processes that would be recruited if actual visual information (i.e. from the outside world) was being processed.

In chapter 5, the dynamics of the onset-phase of psychedelic imagery were investigated. As psychedelic imagery tends to evolve from simple to complex, it was hypothesized that the order of visual regions that will show increased activity after psilocybin injection will be based on the visual cortex hierarchy, from low level to higher level. Though not exactly as hypothesized, some patterns were observed in the beginning of the onset phase in the ventral stream. These patterns were of initial decreases in high level visual areas compared to low level areas. This result suggest that the phenomenological dynamics from simple to complex imagery might be related to an initial ‘deactivation’ of high level modalities, and not to ‘activation’ of low level modalities as suggested in the hypothesis. This result forms a new hypothesis which will be tested in future research. Another hypothesis was that the activity in the magnocellular pathway would precede the activity of the parvocellular pathways. This hypothesis was not supported by the analyses. However, it will be tested again in a future DMT study in which the phenomenological mapping of the dynamics of psychedelic imagery will be done in a more sophisticated way, as in Timmermann, et al. (2018).

Interpretation of the present results regarding psychedelic imagery may be informed by more general research on visual imagery (Kosslyn, et al., 2006; Pylyshyn, 2002). A key question in this research area is whether lower-level stages in the visual system (e.g. the primary visual cortex) contribute to the representation of complex mental images (de Gelder, et al., 2014; Pearson and Kosslyn, 2015). Another related debate is whether primary visual cortex is engaged (Hong, et al., 2009; Miyauchi, et al., 2009) or disengaged (Braun, et al., 1998) during REM sleep. The present thesis addresses a third related question: the role of lower-level visual areas in eyes-closed psychedelic

imagery. The findings imply that low-level components of the visual system (i.e. retinotopically-mapped regions in V1 and V3) are indeed modified under LSD. Moreover, these results suggest that under LSD, the early visual system behaves “as if” it were receiving spatially localized visual information, and that the processing of visual imagery involves other cortical regions as well.

Some interesting questions were not addressed in this thesis. One natural question to ask is whether psychedelic imagery is a top down or bottom up process, and how predictive processing relates to this. While the result in chapter 3 revealed that many cortical regions are involved together with V1 in the processing of psychedelic imagery, it is still not known what the source of this imagery is. In order to answer this question, one must have both high spatial and temporal resolutions with the ability to measure accurately subcortical regions. As for now, there is no technology that can study humans with such accuracy.

Furthermore, it is important to consider that psychedelic imagery has a few distinct temporal phases (section 1.6.4 and 1.6.5) that may be very different from each other biologically. It is possible that simple imagery is a bottom up process with an entoptic origin (Reichel-Dolmatoff, 1975) (Figure 1.12) which is related to the architecture of low level visual areas (Ermentrout and Cowan, 1979) (section 1.9.2), while complex imagery involves a top down process in which high level areas are influencing low level visual areas and incorporating them in the processing of psychedelic imagery. As cortical regions are highly connected in feedback loops and lateral connections, and as 5-HT_{2A}R is abundant throughout the cortex (section 1.5.3 and Figure 1.7), it is possible to hypothesize that the psychedelic experience result from an interplay of bottom-up and top-down processes in which each relay of information between cortical areas is modified through 5-HT_{2A}R. In this case, simple imagery can

transform to complex imagery, while complex imagery still incorporate some geometrical (and entoptic) patterns.

One speculation that I would like to put forward is in regard to the distribution of 5-HT_{2A}R and the way most researchers attempt to explain the experience based on this distribution. Psychedelics might lead to increased irregular excitation, yet high doses or intense moments within the experience might be more associated with inhibition (section 1.8). Some theories suggest that the shamanic and peak experiences relate to intense ergotropic excitation which lead into a paradoxical trophotropic collapse – from sympathetic to parasympathetic (Davidson, 1976; Fischer, 1971; Winkelman, 2010). This notion is strengthened by few studies that show increased power of low frequencies (trophotropic) together with decreased alpha power (ergotropic) (Acosta-Urquidi, 2015; Timmermann, et al., 2018; Winters and Wallach, 1970) (see more on theta frequency in 1.9.5 and 1.9.6). As 5-HT_{2A}R agonists can both excite and inhibit activity and this is dose dependent (section 1.8.2), I would like to suggest that the experience moves gradually from activating different regions to inhibiting them. Therefore, one should not only assume that regions with high distribution of 5-HT_{2A}R are the ones that involved in the psychedelic experience but also take into account the ones with low distribution (such as subcortical regions (Beliveau, et al., 2017)) as these are those which are left after the inhibition of the rest. For example, if one wants to ask about being transported to “another reality” with DMT (section 1.6.4 and 1.6.5), or if one wants to ask about the mystical-type experience (section 1.7), one should consider that the source of these experiences relate to areas with low 5-HT_{2A}R distribution (e.g hippocampus), as all other regions with high distribution have been functionally impaired and the only functioning regions are the ones with low distribution. This model can explain the gradual transition from simple imagery to complex imagery to being transported to a “different reality” to a mystical unitive experience. In this model the visual areas are first excited which leads to simple and some complex imagery, but then they are dysregulated which allows other modalities

to become central to the experience (experiencing “another reality”), and when these modalities are dysregulated, an arguably more primitive or fundamental proto-self remains. If that is the case, that proto-self would actually relate to regions with low 5-HT_{2A}R distribution such as limbic system.

An interesting future avenue which I began to investigate is of the possibility to reconstruct the eyes closed psychedelic imagery based on the fMRI BOLD signal. It has been shown that it is possible to reconstruct a video that a subject sees based on his V1 fMRI activity (Nishimoto, et al., 2011). Furthermore it has been shown that it is possible to predict a painting that a subject imagined based on his fMRI activity (Naselaris, et al., 2015). These analyses used an fMRI analysis technique called “voxel-wise modelling” (Naselaris, et al., 2011) to predict the visual/imagery content of the participants. In the case of the video reconstruction (Nishimoto, et al., 2011), subjects viewed a few hours of youtube videos in the MRI scanner and an algorithm learned how their fMRI signals in the visual cortex were related to the videos. Then, subjects viewed a new video and the *trained* algorithm reconstructed this video based on their fMRI activity. In this thesis it was suggested that V1 is processing eyes-closed psychedelic imagery in a similar manner to regular vision. If this is the case, it might be possible to train the algorithm based on normal vision (youtube videos) without any drug, and then try to reconstruct a video of the eyes-closed psychedelic imagery based on the *trained* algorithm. Furthermore, music can be used to influence psychedelic imagery (Kaelen, et al., 2016), and one hypothesis will be that the reconstruction of the eyes closed psychedelic imagery will be related to the music. To validate this technique, the reconstructed videos will be compared to the reports of the subjective experiences that will be gathered using microphenomenological interviews (Petitmengin, 2006). A successful reconstruction will verify the hypothesis that was laid out in this thesis - that V1 is involved in eyes-closed psychedelic imagery. Furthermore, this type of analysis for other modalities such as language and semantics (Huth, et al., 2016), and applying these methods on these

modalities with psychedelics will increase the knowledge of how psychedelics function in the brain and how they alter consciousness.

By investigating the effects of psychedelics on the visual cortex, one of the more tangible components of the brain, one may be able to extrapolate rules that are gleaned here to the rest of the cortex. For example, increased V1-whole brain RSFC is just one example of a more general rule about increased global connectivity under psychedelics – but it is easier to understand its functional implications when considered in relation to the visual system and the visual experience (Carhart-Harris, 2018; Palhano-Fontes, et al., 2015; Petri, et al., 2014; Roseman, et al., 2014; Tagliazucchi, et al., 2016b). The subjective experience that is closely related to increased V1 RSFC is the experience of psychedelic visual imagery; however, other experiences might be related to other aspects of increased connectivity. We can gain a foothold from understanding that V1 activity and connectivity relate to imagery – and this solid foundation can help us extrapolate to more abstract levels. Furthermore, as the dynamics of the visual experience under psychedelics begin at a low level and evolve to a higher one, understanding relevant mechanism within the visual cortex (which is relatively well understood) might give us clues about more complex mechanisms involving higher cortical systems - which are relatively less well understood - such as the DMN.

7. LIMITATIONS

The Three Oddest Words

When I pronounce the word Future,
the first syllable already belongs to the past.

When I pronounce the word Silence,
I destroy it.

When I pronounce the word nothing,
I make something no nonbeing can hold.

— Wisława Szymborska

This section discuss some limitations of this thesis and other limitations within psychedelic neuroscience. I find it quite important to put into words other limitations of the field, as this thesis is not isolated from other research, as each advancement in knowledge relies on the foundations of knowledge that preceded it. However, there are many limitations of these foundations and it is necessary to state them in order to address them in future studies.

7.1 Head Movement

As mentioned in length in the methodology section, head movement can create strong artifacts in the BOLD signal (2.5.4) (Power, et al., 2012; Power, et al., 2014; Power, et al., 2015). Although preprocessing techniques can help us address these artifacts, it is still the case that in the psychedelic condition, subjects move more than the control condition, and no preprocessing can completely remove this noise. We therefore advise careful selection of subjects for research such as this so as to identify individuals that are better able to stay still within the scanner. Such individuals may be meditators (although meditation can be a confound), highly experienced psychedelic users and/or those experienced with conducting and/or undergoing MRI scans. Another option is to restrict head movement with a head case movement stabilizer, which is tailored for each individual based on his/her own head anatomy ([caseforge](#)) (I have tried already one of these head cases under the influence of DMT and can report that it was very efficient and surprisingly comfortable). One needs to be confident that an individual can tolerate such restriction however, particularly on a potent psychedelic.

7.2 Vigilance

It is suggested that around 30% of subjects fall asleep during fMRI resting state scans (Tagliazucchi and Laufs, 2014). Therefore, some of the results seen in psychedelic fMRI resting state studies could be easily explained by increased vigilance in the psychedelic state compared with the tired placebo state. For example, the reduced BOLD variance under LSD, and the reduced network integration (Carhart-Harris, et al., 2016a), and increased thalamocortical functional connectivity (Müller, et al., 2018), can be easily explained by increased vigilance, as the opposite results (increased BOLD variance and decreased thalamocortical connectivity) are biomarkers of N1 sleep (Tagliazucchi and Laufs, 2014) and reduced arousal (Fukunaga, et al., 2006; Larson-Prior, et al., 2009; Wong, et al., 2013). Therefore, we need to be cautious about inferring that the reported results are absolutely specific to the psychedelic state. Rather, it is possible that they may simply relate to an aroused (in the sense of being more awake or alert) relative to the placebo condition. I believe that this is one of the key limitations of modern psychedelic research. If one wants to investigate the psychedelic state, one must isolate the psychedelic state from other states in which there is an equivalent arousal level but without “psychedelic” components (e.g. visual “hallucinations” and ego-dissolution). One suggestion is to add to future studies another condition of increased arousal, such as administration of a stimulant such as amphetamine, in a dose that produces a level of arousal that is comparable to that of the psychedelic drug state. Interestingly, in the 50’s and 60’s, when the psychedelic research community was much wider, many neuroscientific psychedelic studies have compared psychedelics to stimulants (Aghajanian, et al., 1970; Bradley and Elkes, 1953a; Bradley and Hance, 1956; Brawley and Duffield, 1972; Colasanti and Khazan, 1975; Fairchild, et al., 1967; Foote, et al., 1969; Khazan, et al., 1967; Roth, 1966; Winters and Wallach, 1970).

7.3 Immersion

This limitation, as the one above, is also related to the issue of having an inert placebo condition. The psychedelic state can be highly immersive, and subjects can become highly absorbed into the present moment of experience. One therefore needs to include a condition that is equivalently immersive but not psychedelic. Only by doing this can we isolate the psychedelic component of the experience and extricate it from the immersive component. For example, reduced DMN integration and a relative ‘deactivation’ are seen in many tasks. Indeed, some define the DMN as a task-negative network (Raichle, 2015). Possible control conditions that match the psychedelic experience for “immersion” could include watching a movie or playing a video game for example. Having these control condition will help to differentiate the immersion/engagement component of the psychedelic experience from other components of the experience.

7.4 Activity as Epiphenomenon of Attention

This limitation is more specific to results relating to psychedelic imagery; it was presented first regarding the claim that V1 is involved in the processing of regular mental imagery (Kosslyn, et al., 2006; Pylyshyn, 2002). In this thesis, and in other studies, it has been claimed that lower visual areas such as V1 are involved in processing “psychedelic imagery”. However, the activity and connectivity patterns of V1 might simply be a result of increased attention to the “internal” visual field. That is, while the processing of psychedelic imagery may not be related to V1, the subject may still become more attentive to the visual field and therefore activate V1 - which is sensitive to such an effect of attention. If this possibility were true, then the activity of V1 would be considered to be epiphenomenon of increased attention to the internal visual field. This issue may be addressed in future studies by disrupting the activity in V1 using stimulation (e.g repetitive TMS), and observing any changes in subjective experience of psychedelic imagery. We would predict that such disruption should suppress the experience of psychedelic imagery.

7.5 Heart Rate Variability and Breathing

Both Heart Rate Variability (HRV) and breathing patterns change during the psychedelic experience. The BOLD fMRI response is highly sensitive to changes in HRV and breathing as it depends on blood oxygen levels. Even when HRV and breathing are regressed out of the data as nuisance variables, one cannot completely rely on a completely clean data. Furthermore, HRV and breathing patterns might follow exactly the patterns of the psychedelic experience, especially in short acting psychedelics such as DMT (Timmermann, et al., 2018). Regressing out HRV and breathing patterns can risk removing signal of interest – but this is a cost we must accept if one wants to tease out the drug-effect ‘over-and-above’ the HR or breathing effect. Another way this issue can be addressed is to control for physiological changes by either introducing a control condition that increases the relevant physiological parameters in a similar way to psychedelics, or something could be given or done to moderate physiological effects, such as pre-treatment with a beta blocker that will reduce increased HRV. Granted, beta blockers may have a pharmacology that confounds matters here however, as they interact with serotonin receptors, such as the serotonin 1A receptor.

7.6 Placebo?

It is a known limitation of psychedelic studies that it is difficult if not impossible to find the perfect placebo control condition (Langlitz, 2015). Psychedelic researchers continue to do randomized controlled trials with an inert placebo condition as these are considered “gold standard” by the scientific mainstream. Specific psychoactive drugs produce specific effects in the brain, body and mind and when subjects are asked if they received placebo or psychedelic they are correct in most cases – particularly when doing so for the active drug condition (as is true for most drug studies, including

those with conventional antidepressants for example (Rabkin, et al., 1986)). Furthermore, in a randomized, crossover control trial, if one receives the drug first and knows they receive placebo too, the subject is practically un-blinded about what they will receive in the second dosing session. This is also true to a slightly lesser extent if they receive the placebo first (i.e. a “lesser extent” because its easier for people to be confused about whether or not they’ve received a drug when they receive a placebo). In my view, greater efforts should be made to introduce active control conditions. This would both improve uncertainty about what condition an individual has been allocated to, and also potentially control for confounding variables such as increased arousal. Alternatively, in the context of psychedelic therapy for example, perhaps an argument can be made that positive expectation, which is the basis of the placebo effect, is an inextricable part of any treatment and may even be enhanced by psychedelics (Hartogsohn, 2016) – and thus, considered an active, if not celebrated, component of the treatment model. In modern psychedelic research, methylphenidate (Griffiths, et al., 2006) and niacin (Grob, et al., 2011; Ross, et al., 2016) have been used as active controls in the context of psychedelic-assisted therapy. Future neuroscientific studies should do so as well especially due to the low arousal of placebo compared to psychedelics.

7.7 Phenomenological Measures

In this thesis, ASC questionnaire and VAS questions were used to quantify the subjective effects of drug vs. placebo. However, these measures may have some significant limitations. When viewing the items for simple and complex imagery of ASC it is easy to see that some of them are not phenomenologically specific for a specific dimension. This speaks to a limitation of automated factor analyses for grouping a few items together into a given category and the researchers are then required to name the relevant factor or dimension (Studerus, et al., 2010) - even if, from a phenomenological perspective, the stated category, factor or dimension does

not accurately reflect the given item. The simple and complex imagery dimensions of ASC might have been tested for internal consistency but not for face validity. For example, the item “My imagination was extremely vivid” belongs to complex imagery dimension, yet it could be rated very high even for subjects that had only strong geometrical imagery. The item “I saw colors in complete darkness or with eyes closed” belongs to simple imagery dimension, yet it could be rated very high even for subjects that had only complex imagery. Therefore, the complex and elementary dimensions of ASC are not exclusively measuring what they ought to measure.

In current studies, (Timmermann, et al., 2018), our lab is already using more advanced phenomenological methods such as micro-phenomenology interviews (Petitmengin, 2006) to encourage a more accurate description of the subjective experience, including the temporal dynamics of it. This improved approach should clarify what participants really mean by psychedelic imagery and other aspects of the psychedelic experience - such as the mystical-type experience and ego-dissolution – and also potentially extricate the core features of these experiences from those that are more dependent on individual interpretation, e.g. what is meant by the construct of “ego”.

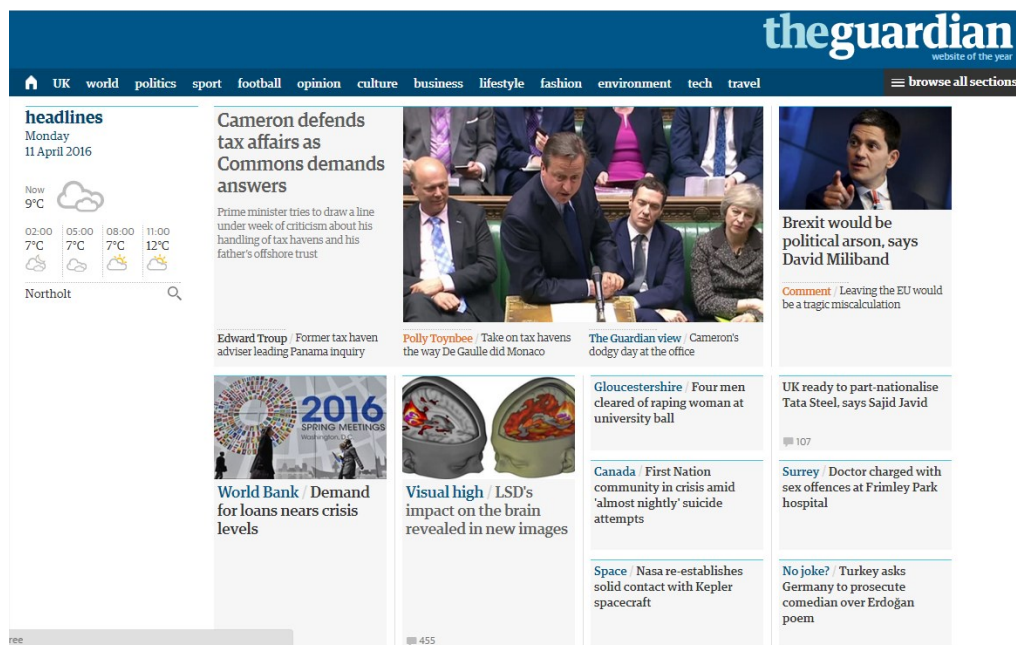
7.8 Phenomenological and Biological Variance

The psychedelic experience is highly varied, and in many respects, unpredictable. It is dose dependent, within each experience there are different phases (section 1.6.4, 1.6.5 and 1.7), an individual’s experience on one occasion can differ much from his/her’s on a separate one, and between-individual differences in what is experienced can also differ wildly. Furthermore, from a biological perspective there are conflicting results regarding excitation or inhibition of neurons (section 1.8), and some human studies show reduced blood flow and BOLD signal in the visual cortex (Carhart-Harris, et al., 2012a) while others show increased blood flow (Carhart-Harris, et al.,

2016a). Therefore, it is difficult to induce any conclusion regarding the mechanism of psychedelics in general based on measures of blood flow or BOLD signal increases or decreases. Measures of network dynamics and electrophysiology however, present a much more consistent picture (Carhart-Harris, 2018). In this thesis, the results in chapter 3 and 4 might be relevant to LSD only in certain doses (low to medium) but not in relation to very high doses. Therefore, the conclusion of this thesis should be limited to 75 µg LSD IV, 90 minutes after injection, and eyes closed. Future studies should expand on this work by trying to capture different phases of the psychedelic experience. For example, one can design a study in which 300 µg of LSD is given, while the subject is waiting for the drug effects in the scanner. As the onset-phase or “come-up” of LSD is relatively slow, one can capture different phases of the experience from simple imagery to complex imagery to mystical-type experience. This will help to determine what the global mechanistic effects of psychedelics are and what effects are more limited to certain phases or doses.

A Note on Media

Just before publishing the results of chapter 3 in *PNAS* (Carhart-Harris, et al., 2016a), I was asked to make a nice figure for *The Guardian*. So I improved Figure 3.1 into a 3D representation of the result. I have to admit that it was quite exciting to work on this figure during the day and to see it by the evening in the website (near some Brexit warnings):



Then this figure started to appear in different websites with different ways of explaining it. The caption of the figure in *nature* was: "Under the influence of LSD, the brain's visual cortex has increased connectivity with other brain regions (right) than when imaged under placebo (left)", which is a fair description. The caption of the figure in *The Guardian* was "Image shows different sections of the brain, either on placebo, or under the influence of LSD (lots of orange)", which is the most accurate description. The caption of the figure in *The Telegraph* was "The image on the right shows how active the brain is when taking LSD", which is a misleading caption as the figure shows connectivity and not activity. The last description took a life of its

own, as different websites described it as activity, and therefore different people contacted me with different theories about why the brain is highly active under psychedelics. The momentary hype around this figure, and some wrong and speculative interpretations of it made me very ambivalent towards it whenever it bounced back at me through my psychedelic social media bubbles. I have learned to be very cautious when I read scientific news and quite critical towards both journalists and scientists that practice sensationalism.

Yet, I have also very much enjoyed being involved in legitimizing psychedelic science, and media exposure is an important part of the work. In the last few years the mainstream media has been turned on psychedelics, and this turned my job from a small niche to something “cool” that many people want to hear about. I have been interviewed in Israel for [*Globes*](#), and [*Ha'Aretz*](#) and when my mother read the interviews she suddenly appreciated my work and listened to the ‘outrageous’ things I say about drugs. Amusingly, it was still me, saying the same things she heard many times before, but now with a public Gushpanka (גושפנקה).

“This is your brain on drugs”

Afterthought on Childbirth

“Pregnant and birthing mothers are elemental forces, in the same sense that gravity, thunderstorms, earthquakes, and hurricanes are elemental forces. In order to understand the laws of their energy flow, you have to love and respect them for their magnificence at the same time that you study them with the accuracy of a true scientist.”

— Ina May Gaskin

My wife, Noa, gave birth to our child, Emanu, on the 8th of April 2018, just after I finished writing most of the Background and Methodology sections of this thesis. The experience in the hospital was of neglect and dehumanization, but despite the challenging setting, we still had one another and I managed to support her with some love and care. She describes her labor experience as a strong out of body feeling together with a paradoxical opposite strong connection to her body – a truly transformative moment. Ina May Gaskin (Gaskin, 1975) criticize the “techno-medical” model of maternity care, and suggest to bring back warmth and love to midwifery: what is the “set & setting” of childbirth?⁵

⁵Ina May Gaskin is a pioneer who teaches our culture about the forgotten ways of natural childbirth. Interestingly, she was married to Stephan Gaskin who was a famous psychedelic hippie in San Francisco in the 60's. Together they opened “The Farm” which is one of the most successful intentional communities from that period. In “The Farm”, Ina May developed her methods and philosophy of natural childbirth. (I would like to thank Ido Hartogsohn for this information).

During my PhD, I have worked in a techno-medical environment, however love and care was given to our subjects and patients as these are essential for the work with psychedelics both in fMRI studies and in psychedelic-assisted therapy. Hopefully, as psychedelic science is mainstreamed, the rest of the techno-medical establishment will learn from it the importance of human connection and gentleness in dealing with any altered-state of consciousness, such as those experienced in different mental health conditions, childbirth, and dying.

“The higher the degree of reality that one attributes to the visions, the higher the likelihood that the visions will, indeed, appear to be real.”

— Benny Shanon

“There is a world beyond ours, a world that is far away, nearby and invisible. And there is where God lives, where the dead live, the spirits and the saints, a world where everything is already happened and everything is known.”

— Maria Sabina

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