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The neuropharmacological basis of psychedelic-induced visual hallucinations

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CHAPTER I. Introduction on Psychedelics

1.1Definition and Classification

Psychedelic drugs consist of a wide class of substances which are mostly well-known for their ability to provoke unique alterations in one's state of mind such as hallucinatory perceptual experiences (most frequently visual) and marked changes in mood and cognition. Surprisingly, compared to other drugs of abuse that have a reinforcing effect, the aim of the assumption of these types of drugs is often to voluntarily access an altered state of consciousness. Moreover, it is not unusual that after the first intake of one of these substances the user avoids the drug, even for a long period of time. That is why they are generally considered to be not addictive. Although nowadays the term "psychedelics" is commonly and interchangeably used to refer to all the drugs that cause the symptoms aforementioned, it is particularly important to distinguish between different classes of psychedelics, as different substances can exert their effect through action on different neurotransmitter systems. The "classic" psychedelics like Lysergic acid diethylamide (LSD), Psilocybin, N,N-Dimethyltryptamine (DMT), and Mescaline are all selective agonists or partial agonists at the 5-HT_{2A} serotonin receptor subtype, they are similar in their structure and in their neurochemical and psychological effects (Nichols, 2016); mescaline is a phenethylamine, while the rest are tryptamines (see Fig. 1.1). On the other hand, other known psychedelics/hallucinogens like Ketamine, Scopolamine and MDMA (ecstasy), have different chemical action sites: ketamine is an NMDA receptor antagonist, scopolamine is a competitive antagonist of the muscarinic type of acetylcholine receptor, and MDMA is either/both a releaser and reuptake inhibitor of monoamines (Advokat et al., 2014). It is also important to note that the term with which all these substances have been classified changed more than once in this field's literature, and it is still controversial. Some of the most used terms (aside from psychedelics) are hallucinogens, entheogens and psychotomimetics. However, each of these terms implies a specific aspect of a drug which is not always accurate (for instance, classic psychedelics do not produce true hallucinations), and often has a negative connotation. Moreover, drugs like scopolamine and ketamine can produce hallucinogenic effects but they differ from serotoninergic psychedelics in having more dissociative effects. In the end, I find more appropriate to use "serotoninergic psychedelics" only to refer to those substances that function as selective agonist or partial agonist on serotonin's 2A receptor, and consequently this work will only focus on them. From now on, just for a simplicity matter, I will use the term "psychedelics" to relate to serotoninergic psychedelics.

1.2 History

Although psychedelics research has less than a century of life, the historical use by humans of these substances (except for LSD) can be traced back to almost 5000 years ago when indigenous tribes started to consume them for religious and medical purposes. For instance, we have anthropological proof of the use of Peyote, a small cactus native to Northern Mexico that contains mescaline, by Aztecs and North American Indians as a sacrament during religious ceremonies (El-Seedi et al., 2005; Bruhn et al., 2002). Similarly, psilocybin (contained in mushrooms) and DMT (contained in a brew called Ayahuasca) were and still are traditionally administered by Aztec shamans during divinatory rituals and in healing contexts (Schultes & Hofmann, 1979; Dobkin de Rios, 1971). The start of recent psychedelics literature can be dated in 1943 when the chemist Albert Hofmann accidentally discovered LSD (Hofmann, 1979). In the following years a lot of clinical papers have been published (Grinspoon & Bakalar, 1979) until when, due to the increasing number of cases of recreational use of psychedelics during the 60's cultural movement, LSD was made illegal, and together with similar psychedelic substances was moved in Schedule I category of abused substances. Currently, we are assisting at a renaissance of psychedelics research, focusing primarily on clinical applications of psilocybin and LSD as a co-treatment (together with psychotherapy) for a variety of mental disorders such as depression, post-traumatic stress disorder (PTSD), cancer-related anxiety, and for detoxification from alcohol or other drugs (Bogenschutz & Pommy, 2012; Grob et al., 2011; Krebs & Johansen, 2012).

1.3 Pharmacodynamics and Pharmacokinetics

As of today, it is extensively recognized that psychedelics exert their neuropsychological effects by activating (as agonists) serotonin 2A receptor (5-HT_{2A}R) both in animal models and humans (Halberstadt, 2015; González-Maeso et al., 2007; Schmid et al., 2015). Indeed, one of the first proofs was a study conducted by Vollenweider (Vollenweider et al. 1998) on healthy subjects where the administration of Ketanserin, a selective 5-HT_{2A}R antagonist, blocked the effects of psilocybin and LSD. This finding has been replicated over the years too, both for hallucinating effects and for inhibition control induced deficits (Kometer, et al., 2011; Quednow, et al., 2012). Moreover, Ketanserin has also been found to hinder the psilocybin-induced lowering of N170 event related potential (ERP) (Kometer et al. 2013), and to block the ayahuasca-induced reduction in alpha power (Valle et al., 2016), both of which are hallmarks of visual hallucinations elicited by psychedelics (see section 2.4, 2.5). It is then intuitive to think that 5-HT_{2A}R agonists

should imitate psychedelics symptoms, but that is not the case: as found by Marona-Lewika and colleagues (Marona-Lewicka et al., 2002) two 5-HT_{2A}R agonists (Lisuride and Ergotamine) did not behave as hallucinogens. To explain this, it is important to know that 5-HT_{2A}R is a G protein-coupled receptor (GPCR), and as G-protein coupled receptors 5-HT_{2A}R can undertake different conformational states, which can be stabilized by different agonists; once this is done the receptor activates only a part of the possible intracellular signaling pathways coupled to the receptor ("functional selectivity") (Urban et al., 2007; López-Giménez & González-Maeso, 2017).

The absorption and metabolism are also similar between different psychedelics, with the exception of DMT which is a fast-acting drug. The usual route of administration is oral through ingestion of the substance, except for synthesized DMT which is snorted or smoked. Generally, mescaline is a bit slower than the others, with absorption in 1-2 hours, an onset at around 3-4 hours and a total action duration that frequently arrive at 10 hours. LSD and psilocybin are usually absorbed within an hour, reaching peak blood concentration levels in 2-3 hours, and the effects last until 6-8 hours. The action of DMT depends on the route of administration: if it's taken alone the first effects occur within 2 minutes and last for 30 minutes; whereas if taken within ayahuasca it has an onset of 30-60 minutes and persist for 3-4 hours. On the other hand, the potency of DMT and psilocybin is approximately similar to one another with a dosage threshold of 0.25 milligrams per kilogram of bodyweight), but very different from LSD (0.02 milligrams per kilogram of bodyweight) and mescaline (5 milligrams per kilogram of bodyweight), being respectively the most and least potent psychedelics (Advokat et al., 2014).

1.4 Subjective effects and the role of context

The most characteristic effects of psychedelics are sensory perception alterations, such as increased sensitivity for all senses, synesthetic effects (mainly audio-visual) and visual distortions (e.g., brighter colors, flashes, geometrical moving patterns, and complex imagery) (Schmid et al., 2015). Nevertheless, their phenomenological profile includes a plethora of effects at multiple psychological levels (a more detailed description of visual hallucinations can be found at 1.6). Indeed, remarkable alterations can be seen in sense of self (e.g., ego-dissolving), mood (e.g., more euphoric/dysphoric or relaxed/stressed) and thought including the perception of reality (changed meaning of percepts) (Studerus et al., 2011). Thus, the user is immerged in an altered state of consciousness (ASC) characterized by the sequence of different stages where the experience can reach several

peak states in which the sense of self is loosened and the ego structure merges in one entity together with the world, giving a unique feeling of unity or "oneness" (Dittrich, 1998). Since the spectrum of subjective experience is quite complex Dittrich designed the "five-dimensional altered states of consciousness" questionnaire (5D-ASC) (Dittrich, 1998), in order to reliably quantify the different psychological effects. Moreover, it has been discovered that the intensity of various dimensions of the psychedelic experience assessed with 5D-ASC questionnaire increased following a dose-dependently trend (Hasler et al., 2004; Studerus et al., 2011) (see Fig.1.2). Nonetheless, it is of utmost importance underlying the influence of context on the user's experience, which can determine the valence of the experience (positive or negative) and, interacting with the dosage, can also shift the intensity of several effects. For instance, assuming psilocybin in a PET scanner increases anxiety levels with respect to a control condition without the PET scanner (Studerus et al., 2012). In the same pooled data analysis, it is shown that 24 non-pharmacological factors played a major role in determining acute responses to psilocybin. These context factors can be internal (expectations, personality, experience) or external (type of environment and culture) to the subject and the psychedelic effect will be dependent on the interactions of those two. As explained in (Carhart-Harris et al., 2018), a party-like environment could have different effects on different people as one could feel too much stimulated whereas someone else could feel safer next to other people. Despite the very strong psychological and perceptual effects these substances do not bring great changes at physiological levels, although it is common to see subtle sympathomimetic changes like slight increase in body temperature, heart rate and blood pressure (Advokat et al., 2014). Furthermore, psychedelics are known for not being addictive and they do not lead to physical dependence (Nichols, 2016). On the other hand, psychological and physiological tolerance is rapidly developed together with cross-tolerance between other psychedelics (Advokat et al., 2014).

1.5 Therapeutic effects and risks

The first application of psychedelic drugs as a therapeutic tool was the use of LSD to treat cancer-related psychological distress (CRPD); in particular, anxiety and depression levels were found to be reduced in two-thirds of the cancer patients (Grof et al., 1973). Clinical applications for the treatment of CRPD have also been recently extended to psilocybin (Griffiths et al., 2016; Ross et al., 2016) which had positive persisting effects on self-report measures of depression and anxiety. There also are multiple suggestions that

psilocybin could be used to treat depression in patients without cancer diagnosis. First, a pilot study reported that a high-dose of psilocybin significantly reduced depressive symptoms for almost three months (Carhart-Harris et al., 2016a). Secondly, an experiment showed that the right amygdala activation of heathy participants, after exposure to both negative and neutral pictures, was markedly diminished and it was positively correlated with positive mood; suggesting that the psilocybin-induced attenuation of amygdala activity could relief depressive symptoms in patients (Kraehenmann et al., 2015). Another tested field of application of psychedelic drugs is the treatment of addictive substances such as alcohol and nicotine. Since the experiments conducted until governments' restrictions did not apply rigorous methodology, the first reliable study that we have is a meta-analysis of six clinical trials which stated that LSD had clinically significant effects on the treatment of alcohol addiction, compared to control treatment (Krebs & Johansen, 2012). Likewise, psilocybin has been proved to have significant clinical outcomes for alcohol addiction (Bogenschutz et al., 2015). Indeed, in this proof-of-concept trial the effects remained for 36 weeks of follow up. Psilocybin has also been tested in a pilot study for the treatment of nicotine addiction, together with psychotherapy (Johnson et al., 2014); at a follow-up of 6 months the 80% of participants showed self-reported and biologically measured abstinence. Despite the great therapeutic potential of psychedelic drugs, it is also important to mention that there are some, albeit very rare, risks associated with these substances. Generally, the acute adverse reactions are of psychological type, such as strong dysphoria and anxiety/panic, which might occur if the drug is taken in unsupervised and uncomfortable settings, and with very high doses. In fact, since the set and setting are crucial for the clinical use these substances, Johnson et al. (2008) developed a safety guideline which recommends a structured use in clinical research and specifies the restrictions that should be followed to minimize adverse reactions. Another psychological adverse reaction is the re-experiencing of visual distortions ("flashbacks") such as afterimages, halo effects, and other visuals encountered during the psychedelic experience. This is known as Hallucinogen Persisting Perception Disorder (HPPD) and, although rare, it provokes functional impairment or distress in social, occupational, or other important areas of functioning (American Psychiatric Association 2013).

1.6 Visual perceptual alterations and Imagery

Since psychedelic-induced visual "hallucinations" are the main psychological effect and their variety is quite large both intra and inter subjects, I think it is important to describe and classify these types of perceptual alterations. Moreover, since there has always been a debate regarding the nature of these symptoms, I find useful highlighting the differences and similarities with psychosis-like hallucinations elicited by deliriants, and with normal voluntary imagination as well. Finally, for reasons of clarity and simplicity, from now on I will use the term 'visual hallucinations' to indicate only those provoked by classic serotoninergic psychedelics, including both visual distortions and induced imagery.

1.6.1 Distinctions with Deliriants

Before the term psychedelic was used constantly, all substances that elicited all sorts of visual distortions or hallucinations were usually called hallucinogens. Although, classic psychedelics visual distortions are not actually true hallucinations (such as those experienced with deliriants and in psychotic episodes), which in fact is the perception of something in the absence of appropriate sensations. Rather, they could be defined as altered perception of real visual objects in any of its visual properties (shape, dimension, movement, depth, color, saliency, etc...), and users are able to distinguish them from real perceptions at moderate doses (Kometer & Vollenweider, 2016). Another distinction regards the content of psychedelic vs. deliriant visions: while deliriants' hallucinations consist of real objects or people that the subject has already seen, psychedelic imagery often resembles surreal or unreal objects, entities, and places; despite having similar vividness (Fortier, 2018).

1.6.2 Psychedelic Imagery vs. Voluntary Imagination

At a phenomenological level psychedelic imagery differs from imagination by having higher vividness, intensity, stability, and spatial resolution over time, furthermore the user has less control over the imagery (Klüver, 1928). Nevertheless, psychedelic imagery and voluntary imagination surprisingly seem to share some similarities at a neurophysiological level. Indeed, a recent review (Fox et al., 2018) of psychedelic functional neuroimaging found that during psychedelic imagery there is an increased activation of the same medial visual area that is activated during voluntary imagination, suggesting that the increased engagement of this visual area is at the base of the higher vividness seen in psychedelic imagery. Although, I suggest that the higher vividness and spatial resolution of psychedelic imagery could be caused by the fact that psychedelics

might involve both bottom-up and top-down processes. Specifically, given that high-level visual areas might have a lower representational spatial resolution compared to low-level visual areas (Jehee et al., 2007), during voluntary imagination (a top-down process) the representation process starts in high-level areas and sends feedforward signals to lower areas, while under psychedelics the imagery process could have its start both in higher and lower visual areas.

1.6.3 Elementary Imagery and Form Constants

In the dynamic of the psychedelic visual experience, elementary illusions are the first ones to appear and at low doses they are featured by higher brightness and contrast of objects and their colors (Siegel & Jarvik, 1975), and the appearance of phosphenes, especially in the periphery of the visual field (Shanon, 2002). At medium doses objects might start to rhythmically drift and vibrate, particularly in their peripheral parts such as the edges (Díaz, 2010). Following the next phases of the experience, new percepts and more complex illusions could appear such as seeing more colors than usual during motion after-images, together with a higher after image suppression of new stimuli (Hartman & Hollister, 1963; Keeler, 1965). Psilocybin can also induce alterations in binocular rivalry (Carter et al., 2007) and disrupted modal object completion of Kanizsa figures (Kometer et al., 2011). In later stages of simple imagery subjects start to see more elaborated patterns of geometrical kaleidoscopic-like figures which are often symmetrical and in movement (Díaz, 2010). These geometrical patterns were systematically analyzed by Klüver (Klüver, 1928; Klüver, 1942), and classified as “form constants” which he found to be peculiar reoccurring geometrical imagery among different subjects (Fig. 1.3). Indeed, these patterns have been subsequently found to be consistent across different cultures and different psychedelics (Siegel & Jarvik, 1975).

1.6.4 Complex Imagery and the role of the Self

Complex imagery, which usually appear after simple imagery, differs from the latter mainly for the content of visions, which is much more semantic (Díaz 2010). First, they occur less frequently than simple imagery (Studerus et al. 2011). Secondly, based on the dosage, they could be seen with eyes-closed or in dark environment (low-to-medium dose), or in a dimmed ambience in the periphery of the visual field (Siegel and Jarvik, 1975). A special exception is reported to happen with DMT (Shanon, 2002) which provoked intense complex imagery even with opened eyes in a bright room. Complex imagery content, in contrast to elementary imagery, is very much dependent on one’s

autobiography, and on set & setting of the experience (Studerus et al. 2011). Indeed, it might contain vivid autobiographical memories (Shanon, 2002), or (especially in ayahuasca rituals) can be composed of non-real entities (gods, demons) or animals, and mystical places (Cott and Rock, 2008).

In Fig. 1.4 and 1.5 you can see how psychedelics imagery has been depicted by several artists after experiencing the visions.

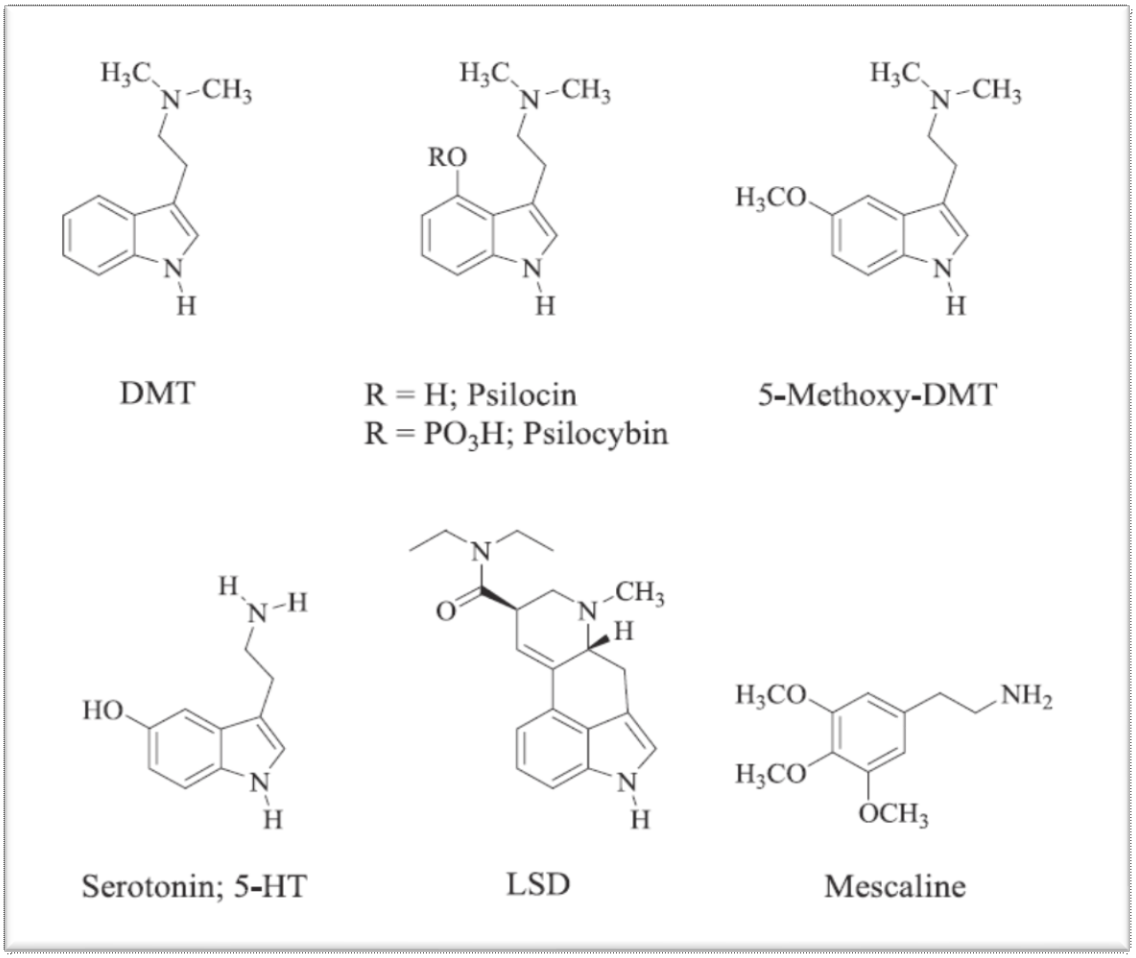

Fig. 1.1 Molecular structure of classic psychedelics

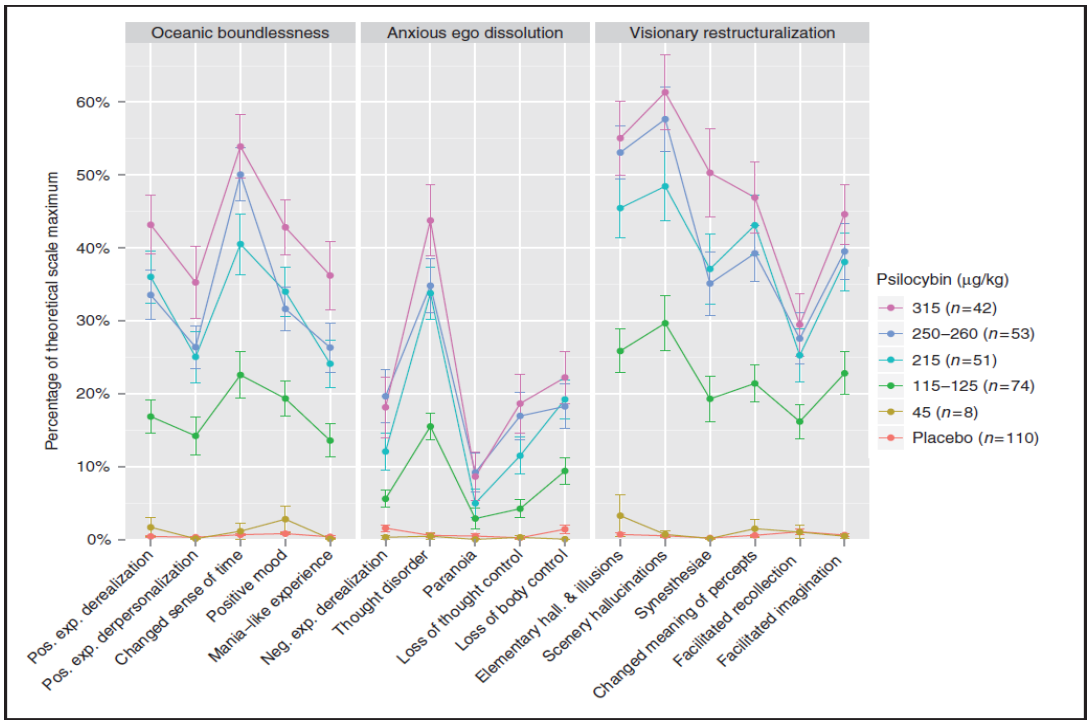

Fig. 1.2 Dose-dependent percentage scores of item clusters from the 'Altered States of Consciousness Rating Scale' (5D-ASC). Error bars represent standard errors. Ratings were obtained during peak drug effects (60–270min after drug administration). From Studerus et al. (2011)

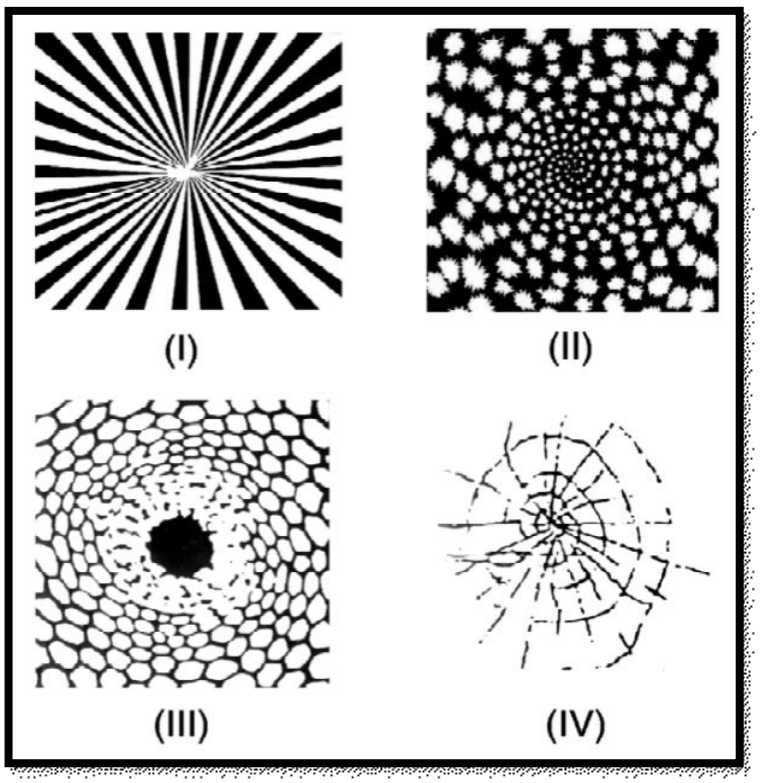

Fig. 1.3 Kluver form constants Klüver's mescaline form constants (Klüver, 1928; Klüver, 1942). I) Tunnels and Funnels; II) Spirals; III) Lattices (e.g Honeycombs and triangles); IV) Cobwebs

Fig. 1.4 Alex Grey & Allyson Grey, Rainbow Eye Ripple, 2019. Acrylic on canvas, 48 x 48 inches.

Fig 1.5 "Los Cachiboleros" by Pablo Amaringo (2002)

CHAPTER II. Neuropharmacological and Neurophysiological Mechanisms of Visual Hallucinations

2.1 Role of 5-HT_{2A}R distribution

Since we now know that 5-HT_{2A}R activation is necessary for the experience of visual hallucinations, it can be assumed that this receptor is densely expressed in the visual cortex. Indeed, although the receptor is generally distributed throughout all the cerebral cortex (Fig. 2.1), it was found that the primary visual cortex (V1) presents a high expression of 5-HT_{2A}R, especially with respect to other secondary areas in the visual cortex (Beliveau, et al., 2017). Within pyramidal neurons of deep cortical layer V are found high levels of 5-HT_{2A}R binding and mRNA expression (Andrade, 2011; López-Giménez, et al., 2001), except for V1, in which the layer with most expression is the fourth (the one that processes incoming input from the lateral geniculate nucleus) (López-Giménez, et al., 2001; Watakabe, et al., 2008). Moreover, the receptor expression in layer VI of V1 was downregulated after three hours of monocular deprivation (Watakabe, et al., 2008). These findings suggest that HT_{2A}R is involved in the very first processing of visual information. Therefore, given these results, the dose-dependent complexity and intensity of visual hallucinations could be explained: elementary hallucinations could be generated by low doses of psychedelics via binding in V1 where there are more receptors, whereas the generation of more complex imagery is provoked by higher doses, needed to bind with less receptors in higher level visual areas. The hypothesis by which low level visual areas are involved in simple imagery while hierarchically higher visual areas are involved in complex imagery is further supported by the finding that different hallucinations elicited with electrical stimulation depend on the site of stimulation (Lee, et al., 2000). It is nevertheless important to highlight that HT_{2A}R is also highly expressed in high-level association areas (Beliveau et al., 2017), such as medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), which are part of the default-mode-network (DMN) and are involved in self-referential thought, semantic processing, and top-down control (Raichle, 2015). In fact, over the last few years psychedelics literature's focus on this network has increased because of the potential role of this structure on the regulation of the psychedelic state, particularly during peak drug effects including "being immersed in another reality", which is thought to be a further step in the complexity of induced imagery allowed by a less pronounced top-down control (Carhart-Harris & Friston, 2019).

2.2 From 5-HT_{2A}R binding to cortical excitation

A big research question has always been whether psychedelics effect on cortical activity is excitatory and/or inhibitory, and recent literature suggest that there is an overall increase in excitation across the cortex leading to a depolarizing effect (Celada, et al., 2013; Nichols, 2016). Given the high expression of 5-HT_{2A}R mRNA in excitatory glutamatergic neurons (Halberstadt, 2015), the most reproduced result is the increment of excitatory postsynaptic currents (EPSCs) of pyramidal neurons principally in layer V (González-Maeso, et al., 2007; Muthukumaraswamy, et al., 2013; Riga et al. 2014). The psychedelic induced increase in excitation is supported by the ability of 5-HT_{2A}R selective antagonists to suppress this excitation (Aghajanian & Marek 1997). Interestingly, the same effect was found also with a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists (Zhang & Marek 2008) and metabotropic glutamate receptor agonists (Aghajanian & Marek 1997). These discoveries indicate that the induced increase in excitation might be due to increased glutamate synaptic activity. In fact, it is thought that a dysregulation in the release of glutamate in the deep layers of the cortex is correlated with asynchrony and temporal dissociation between layer V cell spike activity and the local field potentials' phase ("spike-field decoherence) (Aghajanian & Marek, 1999; Celada et al., 2008). Increased excitation in human visual cortex has been found in an fMRI study assessing visual cortex activation during visualization of eyes-closed visual imagery provoked by ayahuasca (de Araujo, et al., 2012) and psilocybin (Carhart-Harris, et al., 2012). In cats' visual cortex excitation has been found to be increased with low doses of psychedelics, while with high doses there was surprisingly more inhibition (Rose & Horn, 1977). Given that average animal doses usually correspond to higher doses in human experiments, the aforementioned results could mean that inhibitory processes might be seen in humans with very high doses or at peak drug effects. In fact, a phenomenological correspondence is observed when very high doses provoke the visualization of a blackout (Shanon, 2002). This is also supported by the expression (in lower amounts) of 5-HT_{2A}R mRNA in inhibitory GABAergic neurons (De Almeida & Mengod, 2007). Therefore, at this stage of the experience one should also consider those structures that do not express 5-HT_{2A}R (e.g., those that might remain active after inhibition). More information on how psychedelics modulate cortical excitability and how excitation/inhibition provoke visual hallucination can be found in (Watakabe et al. 2009). In this experiment 5-HT_{2A}R agonists induced "bidirectional modulatory effects" on the activity of V1; namely they had opposite effects on high and low neuronal firing rates.

Precisely, they smothered high-firing rate neurons, which are activated by phasic visual stimuli (Montemurro et al. 2008), but heightened the baseline activity (low firing rate) of V1 neurons. Thus, psychedelics can invert the usual processing in V1, shifting the focus on internal background activity and 'neglecting' external stimuli (Kometer and Vollenweider, 2016). In conclusion, it seems that despite the overall increase in cortical excitability, both excitation and inhibition processes are involved in visual hallucinations.

2.3 Mechanistic models of visual cortex activity patterns

In this subsection I will report a computational model of V1 activity under psychedelics that is able to explain geometrical visual hallucinations by building upon V1 topography. Then I will report a relevant experiment, which recorded resting-state functional connectivity (RSFC) within the visual cortex, to integrate its results with the computational models of V1. The model proposed here (Wilson & Cowan, 1972; Ermentrout & Cowan 1979) was the first computational model (a two-layer neural network) that was able to explain elementary geometrical hallucinations such as the Kluver's form constants (especially lattice patterns) building upon a retinocortical mapping of V1, in a way that the activity patterns resembled the form constants. The model by which activity is spread through visual cortex is taken from Turing's mechanism of morphogenesis in which an activator's and inhibitor's diffusion rates determine patches/stripes of activity (Turing, 1952). These stripes of activity, which resemble Kluver's form constants, are represented in the model by the calculation of space constant of excitation and inhibition (Wilson & Cowan, 1972). Thus, geometrical visual hallucinations are explained by an asymmetry between the distribution of inhibition and excitation (more excitation), that brings the tonic activity of V1 to a critical point where the strength with which spontaneous waves propagate through lateral inhibition is increased. This allows more excited neurons to have a greater inhibitory effect on neighboring cells, which are in turn inhibitory, and therefore these last ones will be less inhibitory towards the other neighbor neurons (that are also in turn inhibitory). Given that regular spontaneous activity follows a retinotopic path along the visual hierarchy (Kenet, et al., 2003), this increased diffusion of activity is experienced by the psychedelic user (with closed eyes) in a retinotopic fashion (Ermentrout & Cowan, 1979). Other authors integrated this model with more detailed structure connectivity organization in V1 and were able to predict and describe other Kluver's form constants as well such as cobwebs and spirals (see Fig. 1.2) (Bressloff et al. 2001, 2002; Butler et al. 2012; Billock & Tsou

2012). The way by which elementary geometrical hallucinations are generated in V1 could also be 'extended' to more complex hallucinations that involve higher-level visual areas, as RSFC modulations provoked by LSD matched the retinotopic connectivity structure underlying V1 and extrastriate area V3 (Roseman et al., 2016). The present study specifically found that, during eyes-closed imagery, LSD increased RSFC between retinotopically connected patches of V1 and V3, whereas RSFC was lower between regions that had incongruent retinotopic representations. This result, together with the previously described computational models, suggest that psychedelics turn visual cortex increased activity to be more dependent on its retinotopic architecture, which explains why specific eyes-closed geometrical hallucinations are experienced. This hypothesis could also explain why geometrical imagery is often perceived larger in the periphery of the visual field compared to more foveal regions since retinotopically peripheral areas in the visual cortex have larger receptive fields than foveal areas (Sereno, et al., 1995) (which means they represent a larger space of the visual field).

2.4Brainwaves and reduced top-down control

Brainwaves modulation is perhaps one of the most studied neurophysiological mechanisms in psychedelics literature. The most consistent finding of brainwaves modifications during psychedelic intake is a general smoothing of electroencephalography (EEG) / magnetoencephalography (MEG) signal, especially a marked flattening of alpha frequency (8-12 Hz) power in the occipital cortex (Kometer, et al., 2013; Muthukumaraswamy, et al., 2013; Alonso, et al., 2015; Carhart-Harris, et al., 2016b; Timmermann, et al., 2019) (see Fig. 2.2). Alpha is one of the most studied frequency bands of brain oscillations, and it is known to be involved in the regulation of neurons' excitability levels (especially in visual cortex), by having a strong inhibitory influence (Klimesch et al. 2007, 2012; Mathewson et al. 2011; Foxe & Snyder, 2011). In line with this view, increased alpha power correlated with decreased blood-oxygen-level-dependent (BOLD) signal in visual cortex (Goldman, et al., 2002), while decreased alpha power has been linked to decreased visual thresholds (Ergenoglu et al., 2004; Thut, 2006; van Dijk et al., 2008) and increased firing rates of neurons of the sensorimotor system (Haegens et al. 2011). Hence, since alpha "propagates from higher-order to lower-order areas" (Halgren et al., 2019), it can be assumed that alpha power decrease leads to reduced top-down inhibition and consequent increased excitability in lower-level regions. Indeed, as experimented in a placebo-controlled study with psilocybin (Kometer et al., 2013) that

recorded alpha band activity before and while presenting simple visual stimuli, the psychedelic drug flattened the occipital alpha power that is usually seen in the absence of task-relevant external stimuli in normal conditions (Klimesch 2011; Palva and Palva 2011), and this flattening prevented the stimulus-induced reduction of alpha power which in normal conditions is usually seen between 200-400ms after stimulus onset (Klimesch 2011); therefore creating a dysbalance between excitability levels induced by a stimulus and those that are seen in task-free conditions. A few years later the same author of the psilocybin experiment proposed that psilocybin-induced reduction in alpha power increased the spontaneous activity of the visual pathways (Kometer & Vollenweider, 2016), and that this increase is responsible for the perception of visual hallucinations. Their argumentation is supported by the fact that recorded electrical activity of the visual cortex in resting-state can be approximated to the activity recorded during presentation of simple geometrical figures (Kenet et al. 2003), which means that when this background activity is increased the subject can consciously perceive the geometric hallucinations resembled in visual cortex activity. Moreover, other authors suggested that visual background activity has to be tonically inhibited in order to keep it from being consciously perceived in the form of geometrical hallucinations (Billock and Tsou 2007). Therefore Kometer & Vollenweider conclude that alpha might stand for this inhibitory mechanism, and that under psychedelics intake the lack of this inhibition turns the cortical activity into a background-driven processing mode that gives rise to conscious percepts of visual geometrics. The relationship of alpha power reduction and visual hallucinations is furthermore underpinned by findings of correlations with subjective ratings of the intensity of DMT-induced visual imagery within subjects (Timmermann et al., 2019), as well as with DMT plasma levels after ingestion of ayahuasca (Schenberg et al., 2015). Although the relationship between alpha activity and visual hallucinations is very consistent within the literature, the causal relationship between alpha power and increased/irregular cortical excitation is still under debate. For instance, in trying to assign a direction of causality, by means of dynamic causal modeling, between increased excitability and decreases in broadband oscillatory activity seen with EEG/MEG, the recently developed REBUS model (Carhart-Harris & Friston, 2019) identifies the latter one (particularly alpha) as the consequence of the irregular excitation of pyramidal neurons in deep cortical layers. This is in contrast with Kometer's findings, and therefore more studies will be needed to resolve this issue. Another topic that has been recently re-discussed is whether all of the frequency bands are flattened in EEG/MEG signal. For

instance, theta frequency (2-8Hz) power has been found to be increased in EEG by DMT (Acosta-Urquidi, 2015; Timmermann, et al., 2019), especially in peak-drug states in the second study; and these changes were also correlated with the subjective ratings of intensity. In his review (Carhart-Harris, 2007) Carhart-Harris argues that under psychedelics action bursts of theta activity, generated in the temporal lobes, have been shown to reach association cortices and create new associations which are then brought to consciousness, therefore giving a suggestion of how complex imagery might generated. Additionally, gamma frequency band was found to be moderately increased during psychedelic effects (Kometer et al. 2015; Muthukumaraswamy et al. 2013). Interestingly it can be assumed that, compared to dream states in which gamma frequency is associated with heightened lucidity (awareness of the dream) (Voss et al. 2014), the psychedelic state differs in the level of gamma activity and therefore in the degree of lucidity (which is known to be much stronger). Therefore, even theta and gamma could be implicated in the formation of visual hallucinations.

2.5 Event Related Potentials and High-level vs. Low-level visual processing

Another consistent correlate of psychedelic-induced visual hallucinations consists in dosage-dependent increases/decreases of event related potentials (ERP) over extrastriate visual areas of the brain. With high-density EEG studies (Kometer et al., 2011, 2013) it has been found that the amplitude of medial occipital P1 visual evoked potential around 100ms after visual stimulus onset was dose-dependently increased by psilocybin activation of 5-HT_{2A}R, and this amplification was found to be driven by increased activity in V1 by mathematical source reconstruction. As a result of their experiments Kometer et. al (2011) linked medial occipital P1 psilocybin-induced amplification with subjective reports of increase in brightness perception, based on findings that related brightness perception with medial P1 potential (Proverbio and Zani 2002) and V1 activity (Salminen-Vaparanta et al. 2013). Interestingly, in their second study (Kometer et al., 2013) Kometer and colleagues were able to determine a direct influence of pre-stimulus psilocybin-induced alpha power decrease onto the visual P1 amplification, which could mean that the pre-stimulus induced increase in excitability facilitated the processing of brightness and possibly other elementary visual features in the primary visual cortex. On the other hand, in both aforementioned Kometer's experiments a dose-dependent flattening of N170 visual potential was shown 150-190ms after the presentation of the same visual stimuli. The ERP source locations were the lateral occipital complex (LOC) and the

fusiform gyrus, both of which are known to be part of the ventral visual stream and are involved in the processing of complex visual features (Kourtzi & Kanwisher, 2001; Grill-Spector et al., 2001). In fact, the N170 potential is most notably involved in structural encoding of emotional face expression (Rossion et al., 2000) and object recognition and completion (Murray et al., 2002). The last one in particular is a top-down form of recognition processing that integrates local visual features with stored information to interpolate missing parts of objects (Murray et al., 2002); and in line with this, the processing of incomplete Kanizsa figures evoked a higher N170 amplitude compared to control figures (Murray et al., 2006). Kometer and colleagues (Kometer et al., 2011, 2013) then found that the psilocybin induced N170 flattening, and LOC reduced activity were stronger for Kanizsa figures compared to control figures, suggesting that psilocybin impairs integration processes of object completion. This was then associated with the perception of visual hallucinations since the N170 amplitude smoothing was stronger for higher reported subjective intensity. Hence, by integrating findings of dose-dependent increase in P1 and concurrent decrease in N170, it can be assumed that psychedelics have a double opposite action on low-level vs. highl-level visual processing, namely dysregulating higher-level integration processes (e.g., object recognition, global motion detection), and at the same time enhancing the perception of simple visual features (e.g., brightness, contrast, local motion detection). This hypothesis is supported by behavioral data as well (Carter et al., 2004) which states that psilocybin increased the performance for local low-level motion discrimination and decreased performance for global high-level motion discrimination. The authors concluded that the decreased high-level motion perception could be induced by diminished inhibition of incoherent motion signals. This makes sense, given that pre-stimulus alpha brainwaves support high-level motion perception (Mayer et al., 2016) and it is known that they are flattened by psychedelics. These findings provide a strong explanation for the perception of psychedelics-induced elementary imagery (e.g., drifting of objects and increased afterimage effects), but more information is still needed to better explain the mechanisms of more complex imagery, such as vision of autobiographical memories or never-seen entities/places.

2.6 Changes in functional connectivity

Functional connectivity is a measure of the distribution and flow of information across different areas of the brain, and it is generally operationalized as the "temporal dependency of neuronal activation patterns of anatomically separated brain regions" (van den Heuvel & Hulshoff Pol, 2010). It is usually used to investigate communication flow between different area of interest and therefore it has been used to build different brain networks, ascribe to them functional roles in controlling/processing different brain activity, and to describe connections within one network or between different networks. Resting-state functional connectivity (RSFC) is a method that measures the spontaneous task-free co-activation of different areas of the brain (Biswal, et al., 1995) and it has been recently taken into account to better understand the neural mechanisms of psychedelics, especially at a broader level of action. First, a commonly replicated finding with psychedelics is the increase of functional connectivity between visual circuits and other areas which are usually segregated from them (Roseman et al., 2014; Carhart-Harris et al., 2016b; Preller et al., 2018; Müller et al., 2017) (Fig. 2.3). For instance, RSFC has been found to be significantly increased between higher-order associative networks and primary visual cortex under LSD, together with an increase in cerebral blood flow in visual areas; and these measures were also correlated with renowned reduced occipital alpha power and subjective intensity of visual hallucinations (Carhart-Harris et al., 2016b). However, blood flow increase in V1 was not equally seen in a study assessing acute effects of ayahuasca with single photon emission tomography (SPECT) (McKenna & Riba, 2016). Increased connection of visual networks with higher-level associative systems was also seen with psilocybin (Roseman, et al., 2014) and with DMT (Alamia et al., 2020). In the latter study, DMT effects on 'traveling waves' (cortico spatio-temporal dynamics) were assessed. Based on findings that traveling waves can either represent bottom-up processing by propagating from occipital to frontal regions during visual perception or top-down processing by propagating in a reversed direction during resting states (Alamia & VanRullen, 2019; Halgren et al., 2019; Pang et al., 2020), their result of increased feed-forward (bottom-up) waves and decreased backward waves (top-down) showed that DMT elicited a spatio-temporal pattern of cortical activation that is normally seen under exogenously driven visual perception. This was also supported by a positive correlation between increased feed-forward waves and subjective ratings of visual imagery. The visual cortex was also seen to be more functionally connected with the parahippocampus under administration of LSD together with music stimulation, which

was suggested to be responsible for music-induced imagery (Kaelen, et al., 2016). Furthermore, LSD strengthened RSFC between the fusiform gyrus (an extrastriate region involved in higher-order visual processing) and the thalamus, and this was significantly associated with increased psychedelic imagery measured by the 'visionary restructuralization' scale of the 5D-ASC (Müller et al., 2017). These studies suggest that, given the increased amount of connectivity, visual processing of increased spontaneous activity might be more susceptible to new associations with stored memory and with other sensory modalities as well, which might explain some aspects of complex imagery. Therefore, the communication of the visual cortex with other areas might be a fundamental aspect for the experience of complex imagery given that the level of connectivity is proportional to the intensity of hallucinations. Nevertheless, although visual cortex connectivity changes are of primary interest for the investigation of visual hallucinations and are probably necessary for their emergence, the mechanism by which psychedelics exert their effects is thought to involve many networks and cortical modules, meaning that changes in visual cortex functional connectivity taken alone could not be sufficient to explain visual phenomena. In fact, under LSD and psilocybin, global connectivity increased throughout the brain (Petri et al., 2014; Tagliazucchi et al., 2016), and while networks that in normal conditions are differentiated showed increased RSFC, the connectivity between nodes belonging to the same network is decreased (Carhart-Harris et al., 2016b; Müller et al., 2018; Roseman et al., 2014). This hints that under psychedelics the plasticity of the brain is increased toward a high flexible state where new associations are created, but some of those ones already present might be disrupted, which means that the user is subject to both learning and unlearning. From another point of view, top-down information might be decreased, letting increased bottom-up information to be processed faster and in a non-hierarchical manner. Following this line, in a recent analysis of gradient-based connectivity mapping (Girn et al., 2022) a de-hierarchization of brain networks after both LSD and psilocybin intake was reflected by the levelling out of the principal gradient of cortical connectivity, which represented hierarchy organization from unimodal (e.g., primary sensory cortices) to transmodal brain networks (e.g., associative cortices). The authors also found that this was specifically grounded by a decrease in the modularity of low-order networks (within-network connectivity) together with an increase in the functional connectivity between unimodal networks and transmodal ones (between-network connectivity). Moreover, with the analysis of a second gradient they replicated findings of increased widespread RSFC of visual cortex under LSD. These

findings are corroborated by other studies that show psilocybin-induced diminished activity and within-network connectivity of association networks such as the DMN (Carhart-harris, 2012; Madsen et al., 2021; Müller et al., 2018; Preller et al., 2018), and enhanced sensory brain-wide connectivity induced by both psilocybin and LSD (Carhart-Harris et al., 2012; Preller et al., 2020). Functional connectivity between networks has also been studied with ayahuasca by measuring the transfer entropy, which is a mathematical measure implemented on EEG recordings that establish connectivity directionality and causality (McKenna & Riba, 2016). According to the experiment's results the regular flow of top-down activity from anterior associative regions to posterior sensory-related regions is reversed, and the predictability of anterior areas, based on activity on posterior sites, was enhanced. This had a positive correlation with subjective reports of experience intensity and DMT plasma levels. Summarizing this section, the most consistent finding is the dysregulation of top-down and bottom-up connectivity with a flattening of the regular modularity of the brain structure. Which at a perceptual level means that top-down expectations on external stimuli are decreased, and together with the increased processing of spontaneous activity (allowed by increased connectivity with higher-order networks), this creates both sensorial distortions during perception of external stimuli and visual imagery with eyes closed, whose content will eventually depend on the new connections made in associative networks. Nevertheless, with regard to visual hallucinations, more knowledge on the details of these functional connectivity changes is needed to better understand how simple vs. complex imagery are generated and what are the dynamical mechanisms that underpin the shift from one to the other during phase transitions of the experience.

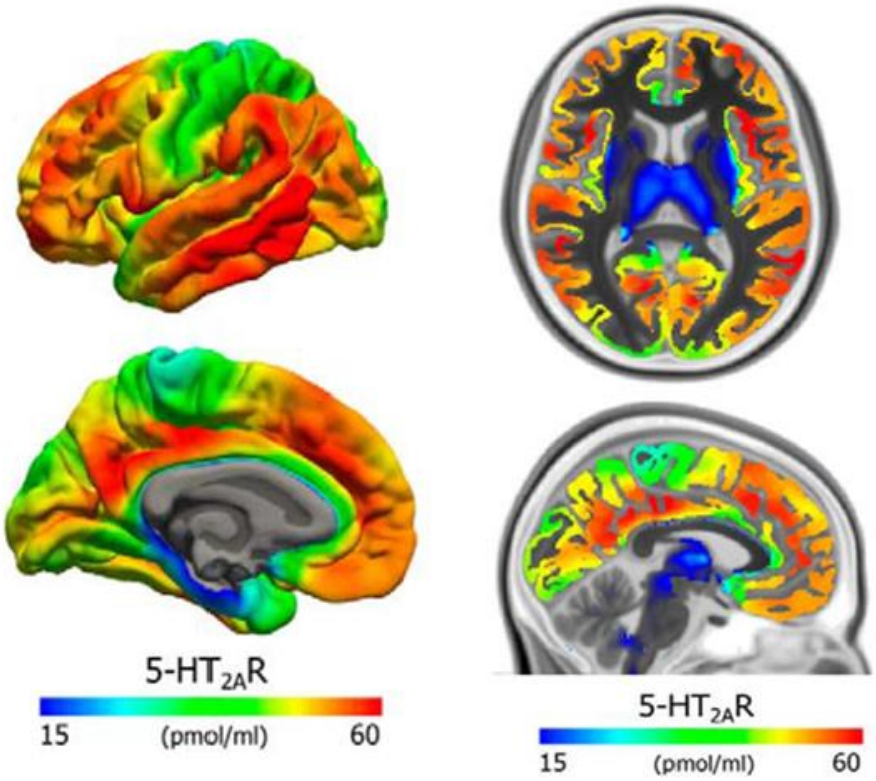

Fig. 2.1 Average density maps for five 5-HT targets. From (Beliveau et al., 2017)

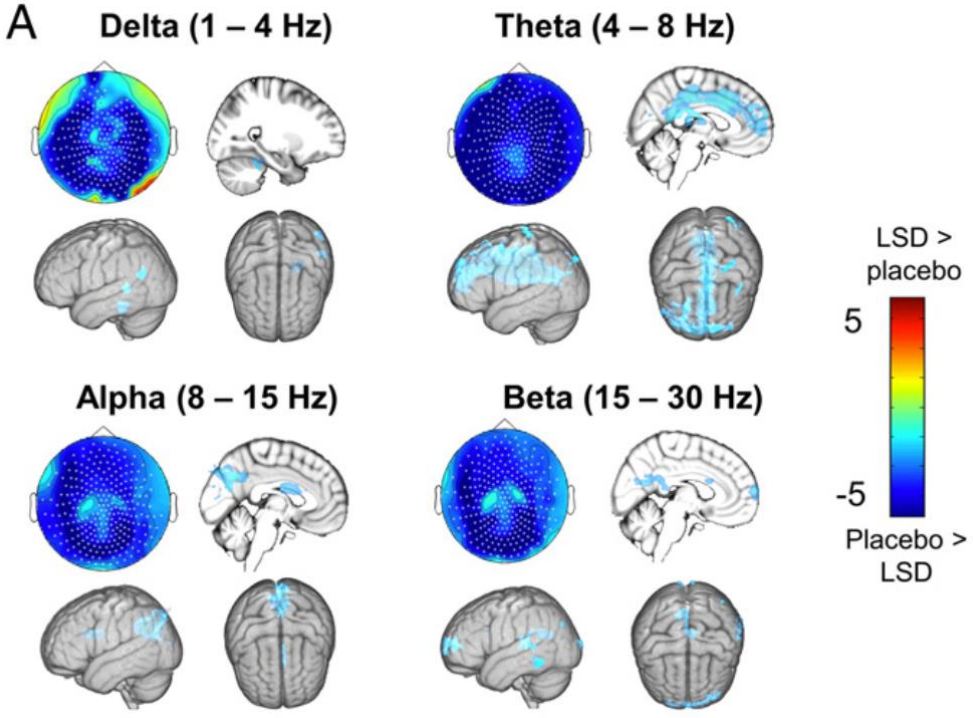

Fig. 2.2 Statistical analysis of planar gradiometer-configured MEG data comparing LSD with placebo in the eyes-closed condition. Blue indicates less power under LSD. Source localization results are also displayed. From (Carhart-Harris et al., 2016).

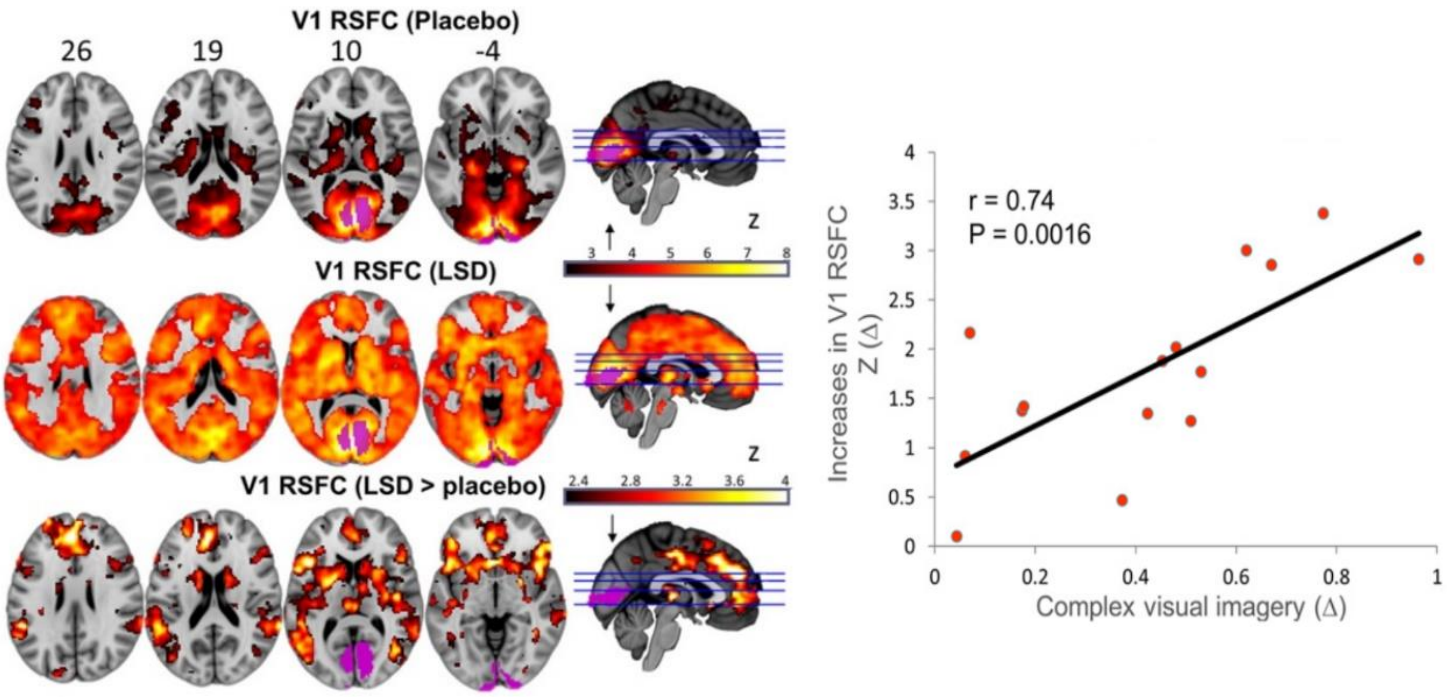

Fig. 2.3 Significant between-condition differences (orange = increases) in RSFC between the V1 seed region (purple) and the rest of the brain. From (Carhart-Harris et al., 2016).

CHAPTER III. Discussion and conclusions

3.1 Involvement of structures and networks in the regulation of synchronization and connectivity

In this section, with the goal to understand the mechanisms by which previously discussed neurophysiological changes induced by psychedelics are generated, I will discuss the involvement of specific structures and networks of the brain (thalamocortical networks, DMN and temporal lobe).

3.1.1 Thalamocortical Networks

Since the thalamus and its nuclei are involved in relaying sensory information to the cortex, acting as filters, and in regulating brain rhythms (Saalmann, 2014; Sherman, 2016; Sherman & Guillery, 2002), the disruption of their activity might result in irregular flowing of information and altered excitability of the cortex. The way by which psychedelics disrupt thalamocortical networks was first descripted in the Cortico-striatal thalamo-cortical model, which explains the known psychedelic-induced perceptual alterations by accounting on the breakdown of thalamic gating function, which in turn lead to irregular coupling and disruption of the networks that connect the cortex with the thalamus and its nuclei (Vollenweider & Geyer, 2001). This is evidenced by the irregular glutamate release in the cortex consecutive to 5-HT_{2A}R binding on the thalamus (Scruggs et al., 2000). A specific structure that might be involved in psychedelic-induced neurophysiological changes is the Reticular Nucleus (part of the thalamus), which GABAergic neurons have been found to be regulated by 5-HT_{2A}Rs (Goitia et al., 2016; RodrÍGuez et al., 2011). The reticular nucleus is thought to control synchronization between brain regions, especially via interaction of low frequencies (alpha) with high frequencies (gamma) (Fogerson & Huguenard, 2016). Interestingly, a study found that in a visual thalamocortical network alpha band activity in the thalamus modulated gamma activity in different cortical regions (Wang et al., 2012), and this modulation was furthermore associated with increased RSFC. This phenomenon is known as Cross-frequency coupling (CFC) (Canolty & Knight, 2010), and another study provided causal evidence that this mechanism is responsible for the modulation of synchronized activity between regions of the thalamocortical system (Malekmohammadi et al., 2015). Taken together, these findings suggest that psychedelics might alter the normal regulation of synchronization driven by CFC, thus possibly explaining results of decreased alpha activity in occipital regions and the increases in RSFC as well. Hence, given the previously discussed correlations between these neurophysiological changes and the

intensity of visual hallucinations, the dysregulation of this process and in particular the reticular nucleus must be taken into account for further research. Another nucleus of the thalamus that might be important especially for visual hallucinations is the Pulvinar, which do not express 5-HT2A mRNA but contains 5-HT2A protein (López-Giménez, et al., 2001), suggesting that it receives input from neurons that contain presynaptic 5-HT_{2A}R. This input probably comes from layer V of the visual cortex given its interconnections with the pulvinar (Purushothaman et al., 2012). Therefore, given the pulvinar's involvement in visual attention and motion perception (Bennett et al., 2019; Saalmann et al., 2012), this could be a possible site of action of psychedelics to induce visual elementary hallucinations.

3.1.2 Temporal Networks/Lobe and Default Mode Network

The aforementioned finding of a correlation between LSD-induced visual imagery and increased RSFC between visual cortex and parahippocampus during music listening could be explained by a loosened control by higher-order associative regions such as the DMN. In fact, parahippocampus share a high baseline connectivity with three components of the DMN, namely the retrosplenial cortex (RSC), the medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC), which have an inhibitory effect (Raichle et al., 2001; Ward et al., 2014). These hubs of the DMN highly express 5-HT2A receptors (Beliveau, et al., 2017) and, consequently to both psilocybin and LSD intake, the RSFC between RSC and parahippocampal cortex (PHC) decreased (Carhart-Harris et al., 2014). What can be assumed is that the loosened connectivity between RSC and PHC could make the latter structure more sensitive to incoming bottom-up information (in the case of the experiment, music). Given that PHC is normally engaged in associative processing of context and episodic memory (Aminoff et al., 2013), under psychedelics action the processing of music might be more susceptible to associations with memories and, given the increased connectivity of PHC with visual cortex, this new associations might activate the corresponding visual representation in the form of imagery. In other terms, listening to music under psychedelics, considering that music itself is a complex stimulus that could even activate strong associations in PHC (especially if the subject has already heard the song), can generate insights which would be accompanied by a visual representation of them. Hence, this could stand for a valid mechanism for the generation of complex imagery. Furthermore, if this is true, then one could hypothesize that the same mechanism is valid for other stimulus-enhanced complex imagery (e.g., through odors or taste).

Therefore, more research is needed to support these neural interactions with more evidence.

3.2 Ending notes on temporal dynamics of elementary and complex visual hallucinations

After reviewing all the possible mechanisms by which elementary and complex imagery might be generated, it is still not very clear what is the mechanism that underpins the noted transition from one to the other. What is sure is that the brain region with the highest expression of 5-HT2AR is V1 and therefore it should be the first target of psychedelics. As mentioned before the psychedelics-induced activation of primary visual areas can be accounted to explain both why and how geometrical imagery is generated, but precise temporal dynamics of neurophysiological changes is missing, therefore we cannot conclude if elementary imagery is first created by increased excitation or reduced alpha inhibition, or even both simultaneously. Despite this, we can hypothesize that the vividness of elementary imagery and the emergence of complex imagery is driven by subsequent action of psychedelics on high-order networks of the brain, such as DMN and temporal networks, with thalamocortical networks that play a role in governing the flow of bottom-up input. In a temporal scheme, the first visual eyes-open visual distortions such as the increase of elementary visual features (color, brightness), could rise from the increased excitability of the visual system and an initial decrease in alpha power, whereas eyes-closed geometrical imagery and fractals could start to emerge when the irregular interplay between visual areas and thalamocortical network nodes reaches a point of destabilization (Kent, 2008); moreover the increased subjective vividness (meant as increased imagination) could be attributed to the increased connectivity of visual cortex with the DMN (Roseman et al., 2014). From then on, the content of complex imagery could be dependent on the new associations made possible by the increased connectivity of visual processing regions with the PHC, while the instability of the imagery could be driven by the increased global connectivity across the entire brain. By contrast, when one reaches peak states, described by a breakthrough experience that marks the passage into a mystical ‘objective’ visionary space in which the subject is fully immersed (Shanon, 2002), the excitability levels might increase until an overload in glutamatergic activity is reached (consistent with reports of sensory overload), followed by a state of lower energy and re-synchronization (Kent, 2008). This is also suggested by Winkelman (Winkelman, 2010), which describes this process as a collapse into a trophotropic and parasympathetic state, also called “rebound to superactivity”, that is usually led by shamanic techniques.

As mentioned in the previous chapter (see 2.4), this trophotropic state might be reflected by the increase of temporal theta brainwaves, which could re-synchronize the activity of different brain regions, giving higher stability and integrity to the visual imagery and a sense of calmness to the user. Therefore, during peak states the visual imagery could have less sensorial richness but an increased integrity and meaningfulness to the user as theta waves spreads from the temporal lobe. The increase in temporal theta activity could be explained by the aforementioned (see 2.2) low density of 5-HT2AR in subcortical regions such as the hippocampus and other temporal structures (Beliveau, et al., 2017). Given that 5-HT2AR regulate both excitation and inhibition (De Almeida & Mengod, 2007), according to the trophotropic state hypothesis these temporal theta-generating regions could be those that are left active after the inhibition of those regions that show high 5-HT2AR density.

3.3 Limitations on psychedelics research

Although the results gathered so fare are promising in the light of a deeper knowledge of psychedelics visual hallucinations, their distinction with psychotic states and their clinical applications, this field's literature shows many drawbacks of various kind, especially of validity and method.

3.3.1 Sample size and representativity

One of the biggest problems encountered in writing this paper was the very little sample size of many of the experiments with psychedelics. Only in (Studerus et al., 2011) there was a high number of participants (N = 110), while the rest of the experiments often have less than 25 participants. Further limitations regard the low representativity of the samples: it is often preferred to select only psychedelic-experienced subjects and exclude naïve ones due to safety reasons related to unwanted psychological reactions. But in doing so the results could be biased by the low representativity of certain personality traits and by the increased tolerance of experienced users; and given that the individual baseline functional connectivity of the brain has been found to be crucial in determining the magnitude of network activity modulations induced by psilocybin (Preller et al., 2020), the low sample representativity could significantly alter RSFC results. Besides, it has been shown that the rare acute adverse psychological reactions in unexperienced users were successfully treated without pharmacological intervention, by supportive interpersonal psychological assistance (conducted following the guidelines for psychedelic research).

3.3.2 Neuroimaging limitations

There are multiple limitations attributable to the use of neuroimaging techniques, especially fMRI, and limitations regarding the analysis of neuroimaging data as well. One of the main problems is the generation of strong artifacts in BOLD signal resulting from head movement during fMRI scans (Power et al., 2012), which is almost inevitable during the psychedelic condition and cannot be completely removed by preprocessing. Another problem arises from the fact that in control conditions about 30% of participants fall asleep during fMRI scans (Tagliazucchi & Laufs, 2014), which means that psychedelic-induced connectivity changes (e.g., thalamocortical functional connectivity) could also be seen due to the increased vigilance compared to control conditions, therefore mining the internal validity of RSFC experiments. In a recent review of 42 research articles studying psychedelic induced RSFC changes (McCulloch et al., 2022) it has been found that data processing and analysis methodology is not shared in any of the articles, except for two. Moreover, networks terminology is inconsistent between most of the papers, and most importantly, only two original datasets constitute the groundwork of more than half of the published literature. Therefore, this lack of original datasets and the great variance in methodology should be tackled with acquiring new data and replicating already published methodologies in order to have more consistency and external validity.

3.3.3 Placebo

The last but not least important limiting factor is the trustworthiness of placebo control conditions. Especially for psychedelics, it is very difficult to erase participants' expectations regarding which condition they're taking part of. Indeed, a recent meta-analysis showed that the intrinsic nature of psilocybin made bliding of participants and lab personnel not possible, therefore strongly increasing the risk for detections bias (Goldberg et al., 2020). One future perspective could be the use of active control conditions such as Niacin (Ross et al., 2016). Although, it is important to highlight that positive expectations play a major role in enhancing therapeutic outcomes and psychedelics could facilitate this effect (Hartogsohn, 2016), therefore the control condition should be based on the context and purpose of the administration.

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