The psychological and human brain effects of music in combination with psychedelic drugs

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“Follow your bliss and don't be afraid,

and doors will open where you didn't know they were going to be”

Joseph Campbell

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Statement of publications

Parts of the data and the discussions presented in chapters 3 and 5 of this thesis have been previously published in *Psychopharmacology* (Kaelen et al., 2015) and in *Neuropsychopharmacology* (Kaelen et al., 2016):

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Statement of copyright

Statement of originality

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All other work reported in this thesis is my own and conforms to the rules and guidelines set out for PhD theses by Imperial College London.

Abstract

This research investigated how psychedelics and music work together in the brain and modulate subjective experience. Chapter 1 highlighted the prominent role of music in psychedelic therapy in the 1950s and 1960s, and how music continues to be used in modern psychotherapeutic trials with psychedelics. Although ‘psychedelic therapy’ shows promising findings for mental health care, little is known empirically about the therapeutic functions of music. The primary objective of this thesis was to address this knowledge gap, via studying the effects of psychedelics and music on human brain function in healthy volunteers, and via studying the subjective experience of music, both in healthy volunteers and in patients undergoing psychedelic therapy.

Study 1 (Chapter 3) demonstrated intensified music-evoked emotions under the classic psychedelic LSD, including emotions of ‘wonder’ and ‘transcendence’. In subsequent work (study 2, Chapter 4), increased activation in the inferior frontal gyrus and the precuneus to the *timbre* features in the music*,* was associated with increased music-evoked emotions of wonder. Study 3 (Chapter 5) demonstrated that LSD and music interact to enhance information flow from the parahippocampus to the visual cortex, and that this effect correlated with increased complex mental imagery and autobiographical memories. Study 4 (Chapter 6), showed that music has a substantial influence on the therapeutic experience with psilocybin in patients with depression, and the quality of the music-experience predicted peak experiences and insightfulness during sessions, and reductions in depression after sessions.

These findings support the hypothesis that the music-experience is intensified under psychedelics, and the widely-held view that this effect may be therapeutically significant. Possible brain mechanisms and therapeutic mechanisms are discussed in Chapter 7, but further research is warranted to better understand these mechanisms, and to learn how music can be best used in psychedelic therapy.

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Glossary

Psychedelics | The word psychedelic is derived from the Greek words psyché meaning "mind" or "soul", and dêlos, meaning "to manifest" or "make visible". Compounds considered "classic" psychedelics include psilocybin (the psychoactive constituent of magic mushrooms), LSD, mescaline (the psychoactive constituent of peyote and san pedro cacti) and DMT (a major psychoactive ingredient in the Amazonian brew ayahuasca). All these drugs share the property of being agonists at the serotonin 2A receptor and have phenomenological similarities. The use of the term 'psychedelics' in this paper refers to the classic psychedelics such as those listed above.

Peak experience | Peak-experiences are characterized by a "transcending" of one's usual sense of selfhood, typically accompanied by emotions of wonder, blisfulnesss and awe (Maslow, 1970). They are often are associated with a sensation of union or completeness, a sense of absence or resolution of inner conflict, and a sense of serenity, confidence and meaningful purpose in one's personal life (Maslow, 1970, Stace, 1970).

“Music may be a human invention, but if so, it resembles the ability to make and control fire: it is something we invented that transforms human life. Indeed, it is more remarkable than fire making in some ways, because not only is it a product of our brain’s mental capacities, it also has the power to change the brain. It is thus emblematic of our species’ unique ability to change the nature of ourselves.”

Aniruddh D. Patel

1 *Background* | Why study psychedelics and music?

Psychedelic drugs and music have a profound capacity to alter consciousness, and have been used by humans for thousands of years and across various cultures. In recent years, increasing numbers of studies have assessed the psychotherapeutic potential of psychedelic drugs, commonly referred to as "psychedelic therapy". Within this approach, music is considered to be an important therapeutic component. The results of these studies are promising, yet so far, the function of music in psychedelic therapy has not been addressed. Increasing numbers of studies have examined how psychedelic drugs and music work in the brain separately, yet so far, no study has investigated how they work together.

The research presented here was founded on the primary motivation to increase our understanding of the therapeutic functions of music in psychedelic therapy, by combining neuroscience and qualitative research methods. Because the subjective experiences of music that are often described under a psychedelic depict a remarkable profoundness, their combined study can prove fruitful as a new research paradigm in itself; one that may significantly advance our understanding of how the human brain processes music, and more broadly, how the human brain produces certain subjective states that are otherwise difficult to access under experimental conditions (e.g. peak experiences and emotional catharsis).

This introduction chapter serves to introduce the reader to the rich history in which this topic is embedded, and to provide a comprehensive overview of the relevant academic literature. In the first half, this chapter will describe the historic use of psychedelics and music, the development of psychedelic therapy in the 1950s and 1960s, and the major perspectives that emerged from this work, including the original motivations for the use of music. In the second half, this chapter will review the recent clinical, psychopharmacological, and neuroscience literature on psychedelics and music, and converge into an outlining of the primary research questions this study aims to answer.

1.1 What are psychedelics?

The term psychedelic was first coined by the British psychiatrist Humphrey Osmond in conversation with the author Aldous Huxley in 1956. Osmond had introduced Huxley to the cacti-derived psychoactive drug mescaline in 1953, after which Huxley wrote the classic book *The Doors of Perception to Heaven and Hell*. Their research and their personal accounts with mescaline, and later with lysergic acid diethylamide (LSD), contributed to the then revolutionary idea in the psychiatric community that changes in mental states are due changes in neurochemistry. Humprhey and Huxley engaged in a quest to replace terms that were previously used for these compounds, such as *psychoto-mimetic* (i.e. psychosis-mimicking compounds) or *hallucinogen* (i.e. hallucination-inducing compounds), with a new term that they intended to be "more inclusive": a term that would not solely describe their ability to elicit psychosis-like symptoms or hallucinations, but also their ability to evoke experiences that have psychodynamic, aesthetic and spiritual significance.

In a famous letter in 1956, Huxley sent Osmond the following rhyme:

> "To make this trivial world sublime, take half a gram of phanerothyme."

Osmond responded to this by writing:

> "To fathom hell or soar angelic, just take a pinch of psychedelic."

The word psychedelic was derived from combining the Greek words *psychḗ,* meaning "mind" or "soul", with *dêlos*, meaning "to manifest" or "to make visible". It refers to the notion that these compounds can bring into the awareness a wide spectrum of latent psychological content, that can both strongly positive or negative in emotional valence – hence the idea that they let the individual who takes them "fathom hell or soar angelic". Osmond presented the term "psychedelic" for the first time at a scientific conference in 1957 (Osmond, 1957), and Huxley illustrated this view in an elaboration on his personal experience with mescaline, in 1954, in his book *The Doors of Perception*:

> "But what I had expected did not happen. I had expected to lie with my eyes shut, looking at visions of many-colored geometries, of animated architectures, rich with gems and fabulously lovely, of landscapes with heroic figures, of symbolic dramas trembling perpetually on the verge of the ultimate revelation. But I had not reckoned, it was evident, with the idiosyncrasies of my mental make-up, the facts of my temperament, training and habits." (Huxley, 1954)

Drugs considered "classic" psychedelics include lysergic acid diethylamide (LSD), psilocybin (the major psychoactive constituent of magic mushrooms), mescaline (a psychoactive constituent of peyote and San Pedro cacti) and DMT (a major psychoactive ingredient in the Amazonian brew ayahuasca). As will be discussed in greater detail in later paragraphs, all these compounds share the property of stimulating the serotonin 2A receptor (Vollenweider et al. 1998; Aghajanian and Marek, 1999). The use of the term "psychedelics" in this manuscript refers to these compounds or to the plants, mushrooms or cacti that naturally produce them.

1.2 Psychedelics and music in pre-historic times

Both psychedelics and music share an interesting history, and one that may be more intertwined than separated. An introduction to the modern study of psychedelics and music may therefore not be complete without connecting it to their rich historical and cultural origins. The challenge with discussions of ancient history lies however in the tendency of the earth to decompose virtually anything in time. This not only renders controlled scientific experimentation impossible, but the little archaeological findings that are well-preserved and successfully uncovered are therefore precious, and also need to be viewed in that respect: They are likely to represent a mere minuscule fraction of everything that once has been. What can we therefore safely infer, without too much speculation, about the historical use of music and the historical consumption of psychedelics?

For music, this task may be relatively simpler, as music-making can (but not necessarily) imply the crafting of musical instruments. Such artefacts are more likely to be preserved than, let's say, a mushroom. Various uncovered stones show modifications that indicate their use as rhythm instruments, such as rasping and drumming. Mammoth bones showing such signs were found along beaters and ivory rattles in Mezin, Ukraine, and dated to 20,000 years old (Lbova et al., 2013; Bibikov, 1978). But the oldest artefacts that have been identified reliably as musical instruments are bone and ivory flutes found in Germany, and these are estimated to be more than 35.000 years old (Conard et al., 2009; d'Errico et al., 2003). Not only is this finding striking because of the age (i.e. these flutes were thus played in a period long before the onset of agricultural settlements, and in a time period where human cave-dwellers shared these untamed natural landscapes with other *hominid* species, such as Neanderthalers); but also, because these instruments are already evident of a remarkable sophistication. The separate holes allow the production of a broad repertoire of auditory pitches. This suggests that humans have likely engaged in musical activities for periods of time preceding the production of these advanced musical instruments.

Indeed, instruments are not necessary to make music, and from records of hunter-gatherer societies across the globe it is clear that, for example, vocalisation and clapping play important roles in a variety of musical activities. In many of these aboriginal societies (e.g., Native Americans, Aka and Mbuti African pygmies, Australian aboriginals and Yupik Eskimos of Alaska), music has strong ceremonial functions, including social, celebratory, medicinal and –particularly frequent- shamanic (Nettl, 1956). The pioneering ethnomusicologist Bruno Nettle was amongst the first to point this out in his book *Music in Primitive Culture*, where he writes:

> "Among many American Indian and some Paleo-Siberian tribes, composition is ordinarily relegated to shamans (medicine-men) or other individuals connected with religion in a particular way. Indeed, musical and religious specialisation are often correlated, and are probably the two activities of primitive life in which specialisation most commonly occurs." (Nettl, 1956)

Nettle also documented the central role of music during shamanic ceremonies of Native American Indians that include the consumption of mescaline-containing cacti. This was soon followed by the documentation the ayahuasca-ceremonies in many tribes in South-America, the mushroom-ceremonies in Central America, Siberia and Papua New Guinea, the Ibogaine-ceremonies in west Africa, the Yopo -ceremonies in the Caribbean's, and so forth (Schultes et al., 2001) - all of which are characterised by the prominent use of music during the ceremonies. Typically, this music consists of lengthily repeated and simple melodic structures, produced via chanting or whistling, and often has significant rhythmic properties, emphasised by the use of rattles, drums or clapping. This simplicity may be, and has been argued to be (Becker, 2004), ideally suited to support the strong introspective altered states of consciousness facilitated by these ceremonies. In these contexts, the music is often considered sacred, only to be used for this purpose, and is associated with the evoking of vivid eyes-closed imagery and powerful emotions. A good example for this is the singing of the "spirit-songs" or *icaro's* that are sung during ayahuasca-ceremonies, of which the anthropologist Marlene Dobkin De-Rios said the following:

> "We could only marvel at the pervasive presence of music in a variety of forms, as an integral part of the psychedelic experience [..] Shamans state that the music they create provokes special types of visions. Healers told me that the particular traditional melodies, icaros, that they choose to sing or whistle, would evoke visions they specifically desired their clients to have, to permit them to see the agent responsible for bewitchment, to resolve anxiety created in the wake of psychedelics use, and so on." (Dobkin de Rios, 2009)

How far do these traditions stretch back into human history? Evidence for the pre-historic use of psychedelic plants, cacti and mushrooms in combination with music-making is elusive. However, their use by hunter-gatherer societies in the modern era is suggestive for their use by earlier communities. Since their natural resources and tool-use are often similar, and thus likely remained static, and given that natural resources and tool-use define cultural lifestyles to a large degree, ceremonial constructs may be preserved for lengthy times too. This argument has been made for the archaeology of music (Morley, 2013), and can equally apply to the archaeology of psychedelics and their combined use with music-making. The ceremonial use of psycho-active plants and music is shown amongst many aboriginal societies on different continents, and may therefore be considered to be as central to human culture as is commonly argued for music alone.

More direct archaeological evidence for the ceremonial consumption of psychedelic plants comes from various uncovered artefacts. Of these, the rock and cave art of the *Tassili n Ajjer* desert in Algeria, dated to be 7000 to 9000 years old, may be both the most ancient and the most mysterious association with psychedelic mushrooms (Lajoux et al., 1964; Samorini, 1992; McKenna, 1993). These include, and are not limited to, a feathered-headed bee-faced figure with mushrooms sprouting out of his body, smiling figures with mushroom-shaped hats running around with mushrooms in their hands, and female figures with round and colourful mushroom-capped faces. Some authors have argued that the vast amounts of geometric drawings found on cave-walls alongside these and other regions, supplements evidence for the authors of these drawings to be in an altered state (Rudgley, 1995, 2014). In a cave in Spain, painted rows of mushrooms were found, resembling locally growing psychedelic mushrooms, and dated to be 7000 years old (Akers et al., 2011). In North America, Texas, specimen of peyote found in caves and rock shelters were dated to be 5600 years old (Bruhn et al., 2002; El-Seedi et al., 2005). Pipes with residues of burned DMT-containing seeds in Argentinia were dated to be more than 4000 years old (Torres, 1998). Many mushroom-shaped stones were uncovered in Guatemala, and dated to be between 3000 to 2000 years old, alongside multitudes of artistic depictions of mushrooms and mushroom-eating figures on ceramics from the same regions and time-periods (de Borhegyi, 1963; Guerra-Doce, 2015).

The Greek gods Persephone and Demeter are depicted sharing a mushroom, and are associated with the then highly popular mystery cult “Eleusis”, in which the participants gathered to share a psycho-active drink called “Keykeon” (Hoffman and Wasson, 2009). The Eastern Vedic hymns are devotions to “Soma”, the “king of all plants”, which supposedly elevated the consumer to become godlike, and some Indian sects maintain the use psychedelic drugs as part of their rituals (Wasson, 1972). Biblical traditions tell the story of Moses who guides the Israelites to find “Manna”, “the bread of god”, which appears as circular disks in the morning dew of the fields, and which would make god visible to the human eye after eating (Merkur, 2000).

Reviewing the various references to the historic consumption of psychedelics in the major spiritual traditions of today, is beyond the objectives of this thesis, but this discussion has sketched out a general message: The uncovering of the various artefacts and the conservation of psychedelic- and music-use in aboriginal societies today, suggest that music-making and the consumption of psychedelics are both ancient and universally human.

1.3. Psychedelics in modern times

Although Europe is home to various psycho-active plants and psilocybin-containing mushrooms, knowledge about psychedelics in modern times only started to break through into mainstream science in the first half of the 20th century. Some argue that the infamous witch-hunts spanning the 15th to the 18th century in Europe played a role in eradicating ceremonial psychedelic-plant use (Rudgley, 2014). The sudden rise in interest in psychedelics in the 20th century was catalysed by (1) the birth of ethnopharmacology, and (2) the discovery of LSD.

One of the most significant contributions for the former, may be the work of Richard Evans Schultes. Via more than 450 publications in the early- and mid 20th century, Schultes increased awareness within the western scientific community about the traditional usages of various psychedelic plants around the world (Schultes and Hofmann, 1980; Schultes, Hofmann, and Rätsch, 2001).

The discovery of LSD centres around Albert Hofmann and his work in Sandoz laboratories in Basel, Switzerland (Hofmann, 1980). In search for a novel blood circulatory stimulant, Hofmann synthesized a range of derivatives from ergot alkaloids in 1938, one of which being LSD-25. On 16 April 1943 Hofmann accidentally intoxicated himself while re-assessing his earlier works with LSD. He felt dizzy and went home. Three days later Hofmann intentionally ingested 250 mcg of LSD, to test whether it was this drug that caused the symptoms he experienced earlier. What he believed would be a miniscule dose, turned out to be what is now known as 10 times the amount of a threshold psychoactive dose. Hofmann described his experience as both frightening and fascinating. After reassurance of his physiological health by his doctor, he described how he experienced “an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscope-like play of colours". But it was what he experienced the day after, that provided an inspiration for the many therapeutic investigations that would soon follow. Hofmann describes in his autobiography that he woke up the next day with a remarkable mental clarity, and wrote:

> "A sensation of well-being and renewed life flowed through me. The world was as if newly created. All my senses vibrated in a condition of highest sensitivity." (Hofmann 1980)

Soon LSD was actively marketed under the name "delysid" to psychiatrists and researchers, as an adjunct for psychotherapy and as a tool to study psychosis (Stoll and Hofmann, 1944). The subsequent paragraphs will provide an overview of the early scientific efforts that followed the discovery of LSD, and the perspectives that grew out of this on its therapeutic use and mechanisms.

1.4 Development of psychedelic therapy in the 1950s and 1960s

Claude and Ey (1934), and Guttman and Maclay (1936) may have been the first to discuss the potential therapeutic use of psychedelics in the academic literature (Claude and Ey, 1934; Guttmann and Maclay, 1936). The study by Guttmann and Maclay (1936) administered mescaline to patients with "depersonalisation", and reported that the patients who demonstrated an improvement afterwards all shared a similar statement about their experience with mescaline:

> "I have seen that I can be as I used to be before." (Guttmann and Maclay, 1936)

Regardless of the infancy of research with psychedelics at that time, this short description already depicted succinctly what would soon be viewed as a principal effect via which psychedelics act therapeutically: their ability to quickly and radically change a person's perspective, leading to sustained changes in outlook, personality, mood and behaviour (Grof, 1980; Grinspoon and Bakalar, 1981). This section will examine the perspectives that were born out of psychiatric research with psychedelics in the 1950s and 1960s, and how this led to the central use of music during psychedelic therapy sessions.

1.4.1 The function of therapeutic experiences

Despite earlier reports on mescaline, it was the discovery of the psycho-active effects of LSD in 1943 that sparked a great international interest in the therapeutic potentials of psychedelics. Busch and Johnson (1950) were the first to report on the therapeutic use of LSD, describing the effects of LSD as increasing the patient's "expressiveness" and as "permitting re-examination of significant experiences of the past, which were sometimes relived with frightening realism" (Busch and Johnson, 1950). This was the beginning of numerous experiments on the therapeutic usage of psychedelics, culminating into an estimated 40.000 patients with mood- and addiction disorders to have been treated with LSD and other psychedelics by the late 1960s (Grinspoon and Bakalar, 1981).

Psychiatrists who performed these experiments noticed that psychedelics can produce diverse types of experiences across patients and sessions. The characteristic perceptual effects of psychedelics are well recognised, but it was other effects, in particular the effects on the individual's emotionality, that ignited the strongest motivation amongst psychiatrists to consider their therapeutic utility. These observations inspired the hypothesis that psychedelics work by weakening the usual psychological defence-mechanisms (also referred to as "ego dissolution"), and thereby uncover (usually "repressed") emotions, memories and thoughts. It was believed this effect of psychedelics would "speed up" psychotherapy.

Eisner and Cohen (1958) reported that under LSD "frequently whole sequences unroll before the patient's eyes as though they had been stored on microfilm" (Eisner and Cohen, 1958). Feld et al (1958) concluded from their observations that "LSD-25 has the astonishing quality of bringing into focus the patient's repressed emotional attitudes, conflicts, etc., and permits their re-activation" (Feld et al., 1958). Abramson (1956) remarked that "emotions hitherto camouflaged were brought out, without the intense guilty fears that had kept them submerged" (Abramson, 1956). And Kurland et al (1971) wrote:

> "The major dimension of drug-altered reactivity with therapeutic relevance is the affective or emotional sphere: intense, labile, personally meaningful emotionality is uniformly produced, with periodic episodes of overwhelming feeling." (Kurland et al., 1971)

Researchers often pointed out the apparent unpredictability and diversity of the emotional effects engendered by psychedelics, and the challenges this brought for therapeutic work. LSD was found to be able to produce states of profound well-being, as well as states of immense anxiety; tranquil states of mind, as well as those riddled with confusion and paranoia; moments filled with intense euphoria, as well as episodes of explosive anger (Terrill 1962). These observations fuelled the emerging view in the psychiatric community that these compounds can produce psychosis-like symptoms. Corresponding to this view, in a series of initial clinical trials, LSD was administered to patients with severe alcoholism with the intention to experimentally induce a "psychosis-like state". It was thought that the LSD-state would to a large extent resemble the alcoholism-induced psychosis, Delerium Tremens (DT), and the hypothesis was that this experience would produce a "psychological shock" that would frighten patients away from their drinking behaviour (Osmond, 1957).

The outcomes of these experiments did however not confirm this hypothesis. First, compared to DT, LSD was found to differ markedly in its capacity to produce a "nebulous sense of wonderment", an increased "aesthetic appreciation" of music and art, an increased perception of "new values", and "a sense of quiet meditation" (Ditman and Whittlesey, 1959). Secondly, out of the variety of experiences LSD could produce, it was not negative or "frightening" experiences that were associated with clinical improvements, but rather the opposite. Patients who showed the strongest improvements, were described to have a certain type of experience that was characterised by such enhanced feelings of "wonder" and a sense of "transcending" their usual sense of self. Unger (1963) stated:

> "Nearly invariably, whenever dramatic personality change has been noted following the use of these drugs, it has been associated with this kind of experience, that is one called transcendental or visionary" (Unger, 1963)

And Terrill (1962) noted:

> "When therapeutic changes did occur, they were often of a qualitatively different order than those which occur in traditional psychotherapy. Under the influence of LSD, the individual goes through highly intense and unusual experiences which may very well change the way in which he views life" (Terrill, 1962)

Psychedelics were found useful by psychiatrists not only for their acute psychological effects, but in particular for their capacity to facilitate enduring therapeutic change after the session, ranging from weeks, months, or longer (Terrill, 1962; Unger, 1963; Kurland et al., 1971). The type of experience under LSD that was found to promote such therapeutic changes most reliably, were argued to exhibit this "self-transcending" quality (Kurland et al., 1971). It were these experiences that were thought to allow the individual to obtain a sudden shift in perspective on themselves, charged with emotionality, motivating a change in behaviour accordingly (Savage, 1966). The general consensus arose that it was *not* the drug, but the *experience* that the drug can facilitate, which is therapeutic (Hoffer, 1965). By the mid 1960s, researchers identified the types of experiences that were considered most therapeutic, and these can be roughly classified into two main categories (Schmiege, 1963):

1) Autobiographical experiences: characterised by an emotional "release" or "catharsis", the experience of vivid and emotionally charged personal memories and insights into one's own personal life. These experiences were often interpreted within a psychodynamic framework.
2) Peak experiences: characterised by a sense of dissolving or transcending one's sense of usual self, culminating into a sense of union, and feelings of bliss and spirituality. These experiences are sometimes also referred to as "spiritual-type experiences", "mystical-type experiences", or "psychedelic-peak experiences", and were often interpreted within a humanistic framework.

1.4.2 The function of non-drug variables to facilitate therapeutic experiences

An increased awareness emerged of the influence that non-drug variables have on determining the types of experiences patients undergo (i.e. variables other than the drug, such as social atmosphere, the music, the physical environment, etc.) (Unger, 1963; Fox, 1967; Kurland et al., 1971; Grof, 1980). This is now commonly referred to as the importance of "set and setting", where set refers to the mind-set of the individual, including its personality, mood and expectations, and setting refers to environment in which the drug is taken, including its interpersonal- and sensory- qualities (Johnson, 2008).

Psychiatrists began to experiment with a strategic design of non-drug variables in order to promote most desirable therapeutic experiences and outcomes. One leading example for this course in history was Humphrey Osmond, who arrived in 1951 at the Weyburn Mental Hospital in Canada, to be shocked by the “bleakness” of the institution. Osmond engaged with an architect, Kiyoshi Izumi, who, after his first personal experience with LSD, set off to design a new psychiatric hospital, that eventually was recognized by the World Health Organisation for its highly innovative quality (Dyck, 2010).

Chwelos et al (1959) summarised the growing awareness on the significance of the setting as follows:

> “We had noted before from our studies of the psychotomimetic properties of this drug that the environment and particularly the attitude of the people around the person undergoing the LSD experience seemed to influence his reaction profoundly. […] The environment surrounding the patient taking LSD was changed by the addition of auditory stimuli, visual stimuli, emotional stimuli and a change in the attitude of the people in contact with the patient.” (Chwelos et al., 1959)

A particular strong example of this attitude towards designing setting-variables in service of the therapeutic experience, is represented by the psychiatrist Van Rhijn (1960), who stated:

> “So far, as Dr. Abramson clearly outlined, we have used frames of reference in which LSD is used as an aid to psychotherapy. However, within our frame of reference […], psychotherapy is used as an aid to the LSD experience. Our objective is to give each patient a particular LSD experience. To this end, we use psychological and environmental tricks: sound and music; visual stimuli, such as paintings by Van Gogh; tactile stimuli, such as various smooth or rough objects for the patients to handle. We also take advantage of the heightened suggestibility of the subjects by using persuasion, suggestion, and reiterated demand, with the theme of hope and possibility of change.” (Van Rhijn, 1960)

The increased emotional responsiveness under the drug, was not seen as an obstacle, but as an effect of the drug that can be utilised in service of therapeutic objectives. This was attempted by tailoring the design of non-drug variables such as the environment and the music being played, in such way that these variables become an active part of the therapeutic sessions. By the late 60s, the foundation of psychedelic therapy was characterised by a strong patient-centred approach, adapting setting-variables to patient's therapeutic needs, to maximise the occurrence of autobiographical- and peak experiences (Fox, 1967).

1.4.3 Psycholytic therapy and psychedelic therapy

At that moment in time, by the late 1960s, broadly speaking two different therapeutic approaches had evolved via which these views manifested into practice: the "psycholytic" method, mainly practiced in Europe, and the "psychedelic" method, mainly practiced in the United States. These approaches differed in the dosages administered, the amount of sessions conducted, and the structure of the sessions themselves (Grof, 1980):

1. Psycholytic therapy was characterised by lower dosages, with the intention to preserve sufficient "ego-functioning" for the patient in order to actively engage with the therapist during the sessions. Generally speaking, the primary goal here was to use the drug as an adjunct to psychotherapy, with the emphasis on facilitating "autobiographical experiences". Typically, patients underwent multiple psychedelic-assisted therapy sessions to reach the therapeutic objectives. Music was often used in psycholytic approaches, but more frequently intermitted by conversations or periods of silence.
2. Psychedelic therapy was characterised by higher dosages, with the intention to dissolve "ego-functioning", and for the individual to "immerse" fully in the unfolding experience. The primary goal here was to facilitate a "peak experience" that would result in enduring changes in personality, mood and behaviour. Typically, patients underwent one or a small number of sessions, and would listen to music for the majority of the time during these sessions - often with eyes closed to increase introspection.

In practice, autobiographical- and peak experiences often co-occurred within both psycholytic and psychedelic methods, and within one session. A good example of this can be found in an excerpt from a case reported by Kurland et al (1967), describing the treatment of a patient with alcoholism with a high dose of LSD (450 mcg). This excerpt demonstrates the use of various therapeutic elements that have been discussed here, such as the significance of both autobiographical and peak experiences, and how the therapists utilises non-drug variables to provide adequate therapeutic support:

> “I was now very conscious of the fact that the music was creating variations of great beauty in my mind. It was such beauty that words can't describe it. The word "magnificent" kept running through my mind. I felt that I was being overwhelmed by beauty. I stated that I was undergoing the most magnificent experience of my life.
>
> By this point, I had lost all sense of time. What seemed like an eternity later, but possibly only a minute or so in actual time, I became aware that my mood had changed. I suddenly saw myself near the bottom of a huge filthy pit. It seemed to be bottomless and was crawling with horrible things such as octopi and enormous, odd-shaped frogs. I tried to crawl my way out of the pit and finally got near the top. Looking down, it was horrible - worse than I have ever visualized hell. Huge vats and casks containing whiskey were being poured into this slimy pit. It seemed that all the whiskey in the world was being dumped there. I began to cry. A feeling of deep guilt and remorse had come over me. The doctor had me sit up. In discussion with him, I realized the significance of this episode for my own experience with alcohol. After my crying spell, I felt relieved and cleaner inside.
>
> Once again I reclined on the couch. The music became more meaningful to me than anything I had ever heard before. A tremendous feeling of exaltation came over me. It kept growing in intensity. I felt rapture and ecstasy. Each moment I thought I had reached the zenith of rapture and joy; then the intensity and ecstasy would increase. It was overwhelming! There are no words to describe my feelings.
>
> Then, while I was in this state, all became still and quiet. A sense of cleanliness and purity swept over me. I was alone and at peace. At this precise moment, I felt that all was holy and pure. I felt humble and insignificant. I was completely awed! It was the greatest, most magnificent experience of my life. I knew then that life has meaning

> and riches and rewards. I felt as though I had been reborn. Probably never again will I undergo such an experience. But I don't care – once in a lifetime is more than any mortal can hope for. I then began to think about mankind in general. I realised that what I had experienced was potentially in everyone, and I felt compassion, warmth, and understanding for my fellow man. […] I cried. I remember wishing that my wife could be at my side, so I could tell her and show her how I now felt. I knew then that I had been throwing my life away, and that there was so much I could do to change things for the better." (Kurland et al., 1967)

1.5 The use of music in psychedelic therapy in the 1950s and 1960s

The realisation that non-drug variables (for example, the physical environment, the social environment, the mind-set and the music) assubstantially influence the patient's experience under a psychedelic, was typically explained as the result of a "weakening" effect of the drug on the patient's psychological defence mechanisms. This would lead to an enhanced suggestibility and emotional response to various types of stimuli from the environment. From early on in the scientific literature, descriptions appeared that called attention to the particularly remarkable influence of music. Cutner et al (1959) describes the relationship between ego-boundary dissolving effects of LSD and the intensified response to music as follows:

> "The most impressive feature in the experience of the non-rational system was the disappearance of all boundaries between individual entities, or, indeed, the disappearance of individuality as such. […] In this way, the meanings of certain musical phenomena (rhythms, intervals, etc.) were felt to have their exact equivalents in certain tensions or experiences of pressure, movement or position of certain parts of the body." (Cutner, 1959)

In the efforts to provide optimal therapeutic support for patients via design of setting-variables, a striking consistency appeared in the literature around the use of music. Therapists frequently emphasized the significance of playing music. In general, the reasons to incorporate music within psychedelic therapy were described as (1) music's capacity to modulate emotion and mood, (2) music's capacity to evoke autobiographical memories and to stimulate the imagination, and (3) music's capacity to facilitate peak experiences (Bonny and Pahnke 1972; Grof, 1980). In what follows, these separate points will be discussed.

1.5.1 The use of music to facilitate emotion

The perceived value of the emotion-modulating effects of music are well described by Holzinger (1964), who stated that the patient's ability "to regain fully his emotional expressive abilities" under LSD, "negatively, and especially, positively" to be one of the most important therapeutic mechanisms within LSD-assisted psychotherapy. Holzinger continued to describe the main role of music as "to enhance this ability of the patient to express his feelings" (Holzinger, 1964).

Eisner and Cohen (1958) wrote that music was used "initially to aid in relaxation", but that it was soon realised that music could support the therapy sessions in different ways too:

> "After repeated observations that music seemed to potentiate the drug action, it was used when there was no verbal exchange. Selections of the patient's choice or of a semi-classical nature were played during the early phase; certain piano concertos were used at the height of the experience". (Eisner and Cohen, 1958)

This point is illustrated especially clearly by Butterworth et al (1962), who reported the use of music to intentionally evoke emotionally intense experiences:

> "After the initial and usually apprehensive episode, an attempt is made to send the patient into an intense episode. Factors encouraging such an episode are: reassurance, selection of meaningful music, absolute quiet and privacy, with discouragement of any analysis and discussion of the episode while it is in progress." (Butterworth, 1962)

Hoffer (1965) noted that music can "be very helpful", but that music and other non-drug variables factors "must be looked upon as aids and not as objectives of the experience", and that the music should always be tailored to every patient's unique needs:

> “Some subjects find music intolerable and visual aids repulsive, and their wishes and feelings must be honoured. They find music extremely distracting and it prevents them from fully experiencing other components of the reaction.” (Hoffer, 1965)

Hoffer continued to explain that the effects of LSD on altering the perception of music and the emotional response to music, can however be utilised strategically to facilitate intense emotional experiences with high therapeutic significance:

> “Very often, sounds which normally have no particular aesthetic appeal, were heard in a most unusual manner. Subjects who were indifferent to music, were enthralled by it. One of our subjects, a physicist, was overwhelmed by the beauty of music being played on an old scratchy record player. After a while he exclaimed *“I wish they could play it as beautifully as I now hear it.”* The background noise of the record did not reduce his appreciation of the music. This property of the experience is very useful in bringing out the psychedelic reaction. Carefully selected music can be very powerful in altering the subject’s mood and associations. One subject, an intellectual, cold physician, who was an alcoholic, did not have any emotional reaction to 300 mcg of LSD for about 2.5 hours. When Ave Maria was played, he seemed startled, then in a few minutes, became transfixed with emotion and began to cry. The song had suddenly taken him to his youth when he had been very happy. The music triggered of an emotional catharsis which completely altered a psychotomimetic to a psychedelic experience.” (Hoffer, 1965)

1.5.2 The use of music to facilitate autobiographical experiences

As the previous section showed, the evoked emotionality by the music during the peak of the drug-effects were often found to be of autobiographical meaning. Psychiatrists typically reported a blending of vivid memories and personal thoughts with strong feelings, such as in the following statement by Sandison (1963):

> “The immediate result of giving the LSD is to produce a deepening of the patient's emotional tone, a change in thinking, sometimes regression to an earlier emotional

> and intellectual period and the reliving of emotionally charged memories.” (Sandison, 1963)

The first clinical observations that patients under LSD remember past events in “frightening realism” (Busch and Johnson, 1950), and that not infrequently “whole sequences unroll before the patient's eyes as though they had been stored on microfilm”, was a major incentive to explore LSD’s potential therapeutic use further. Subsequently, music was found to be in particular helpful to exert a degree of guidance in this phenomenon. This is well summarised by Chandler and Hartman (1960), who said:

> “Music can be an effective stimulus in helping to bring out affectively charged memories and fantasies. We have found classical music generally best, although a great variety of different kinds of music can be effective, especially if the music can be selected in terms of specific aspects of the patient's emotions and background. Music was played throughout the sessions as "background" and sometimes with the instruction to "go with the music" and to have fantasies suggested by the music.” (Chandler and Hartman, 1960)

The main view behind the significance of these autobiographical experiences, was that they facilitate a state of personal insightfulness, characterised by new perspectives on oneself and on one’s life, that promote changes in the way the person subsequently lives his or her life. Smith et al 1959 described that “It is hoped by this method to make the experience a thought-provoking one rather than a frightening one” (Smith, 1959). The authors illustrate their appraised therapeutic benefits from the effects of LSD and music via the report from a 39-old alcoholic patient, describing his therapy sessions with LSD as follows:

> “The experience I have had as a result of the drug was unique and most definitely constructive. It manifested itself in many ways, the most important being my ability to recall certain events, some pleasant, some very unpleasant. It allowed me to see myself as I really am, as a person who is first an egotistical deceitful procrastinator and have many more defects which I am aware of but, because of my lack of

knowledge or something or other, have never been able to do anything about.” (Smith, 1959)

1.5.3 The use of music to facilitate peak experiences

Music played a particular central role in the “high-dose” psychedelic therapy approach. After administration of the drug, patients were typically encouraged to fully direct the attention inwards and listen to a music playlist for the subsequent 6 to 8 hours (Grof, 1980). This approach was heavily influenced by Helen Bonny, a music-therapist, and placed a significant emphasis on music’s capacity to facilitate peak experiences:

> “The time of peak drug intensity when psychedelic peak experiences are most probable comes 3 to 5 hours after ingestion. The greatest effort is made to provide an optimal setting for this type of experience. It is for this period that there is the greatest agreement among therapists regarding the type of music to employ. […] As this is the most critical period of the session, a discussion of appropriate and inappropriate ways in which music can be used is especially important. In the repertoire designated as ‘peak music’ are certain selections which have been shown by experience to evoke powerful emotions and to aid greatly in facilitating the occurrence of peak experiences if played at the proper time. If these selections are played at an improper time, the potential effect can be wasted and a negative musical imprint for that particular selection may result.” (Bonny and Pahnke, 1972)

The use of music to facilitate peak experiences derived significant inspiration from humanistic psychology, and in particular the views pioneered by Abraham Maslow, who argued that peak experiences are integral to the lives of healthy *self-actualising* individuals. Maslow said the following about psychedelics:

> "In the last few years it has become quite clear that certain drugs called "psychedelic", especially LSD and psilocybin, give us some possibility of control in this realm of peak experiences. It looks as if these drugs often produce peak experiences in the right people under the right circumstances, so perhaps we needn't wait for them to occur by good fortune.” (Maslow, 1964)

At the time that the work by Bonny and Pahnke (1972) was published, new government regulations were already put in place (by 1966 in the US, and by 1967 in Europe) that marked the beginning of a long hiatus in research with psychedelics. Although the intentions behind these regulations may have been to halt the growing uncontrolled use of psychedelics in society, what was truly halted was the scientific research (Nutt et al., 2014). It took several decades for academic human research with psychedelics to restart. The subsequent paragraphs serve to provide an overview of this recent *renaissance* of modern research. It will show that the therapeutic approaches employed in modern studies with psychedelics, are heavily influenced, if not fully compatible, with the views that were developed by the 1960s as outlined above.

1.6 Modern psychological and psychotherapeutic research with psychedelics

The level of interest today, in studying the therapeutic potential and the human neuroscience of psychedelics, stands in stark contrast to the almost complete absence of this research in the preceding decades. This revival is posing a number of important questions for the scientific and psychotherapeutic community. As was detailed in the previous section, psychedelic therapy differs from current treatment approaches on several major points. Compared with conventional pharmacotherapy (i.e. psychiatric medication), the strongest contrast is that in psychedelic therapy the aim is not to administer the compound repeatedly and continuously, but only on one or a few occasions, with the objective to facilitate sustained improvements (i.e. clinical remission that extends beyond the acute drug effects during the therapy sessions). Compared to conventional psychotherapy, the strongest contrast is, first of all, that a drug is administered, and secondly, that this drug has powerful acute subjective effects: The lengthily periods of introspection and intense emotionality facilitated by psychedelics do not merely aid the usual way psychotherapy is performed, but instead yield dramatic consequences on the way the therapeutic sessions are performed, including their structure, duration and the role of the therapists.

The views that led to the development of the procedures that characterize psychedelic therapy sessions in the 1950s and 1960s, are to a large extend derived from direct clinical observations, case studies, or experiments that were not well-controlled. In addition, the practice was often informed by theoretical frameworks that are not always supported by sufficient scientific evidence. One example of this are psychodynamic hypotheses around ego-functioning, and the then-popular idea that psychedelics weaken "ego-defence mechanisms", resulting in a regression to an earlier emotional and intellectual mode of cognition. This has led to a therapeutic method that is construed from various concepts and assumptions that await empirically validation.

Addressing this is important, given psychedelic therapy receives an increasing amount of empirical support for its safety and efficacy, and is being implemented at increasingly larger scales in the years ahead (i.e. larger numbers of therapists and patients will be working within this therapeutic framwork). Studies are therefore warranted that not only establish safety and efficacy of the procedures, but also scrutinise the assumptions inherent within these procedures and to further an empirically grounded development of the therapeutic working model.

These considerations were a central motivation for the research presented in this thesis. Given the primacy of music during psychedelic therapy sessions, the focus was on studying the combined effects of psychedelics and music. In order to formulate the primary research questions this research aims to address, this section will provide an overview of the modern pre-clinical and clinical human research with psychedelics, and highlight how recent research has addressed some of the observations and interpretations reported in the 1950s and 1960s. In summary, these are (1) the variety of subjective effects of psychedelics (hence, leading to a need to structure the experience), (2) the effects of psychedelics on emotion and mood, 3) the effects of psychedelics on ego-functioning, (4) the capacity of psychedelics to evoke autobiographical experiences, and (5), the capacity of psychedelics to evoke peak experiences. This section will conclude with a review of the recent clinical trials with psychedelics. See table 1.1, for methodological details regarding these referenced studies.

1.6.1 The variety of subjective effects of psychedelics

Several modern studies have investigated acute subjective effects of psychedelics in healthy volunteers using questionnaires and behavioural experiments, demonstrating that they can occasion changes in perception, cognition and emotion (Vollenweider et al., 1998; Carhart-Harris et al., 2011; Kometer et al., 2012) and in a dose-dependent manner (Carhart-Harris et al., 2011; Hasler et al., 2003; Griffiths et al., 2011). The acute subjective effects of psychedelics are often assessed via the altered state of consciousness questionnaire (ASC), that measures changes in distinct factors of conscious experience (Dittrich, 1998; Studerus et al., 2010). One major factor of effects of psychedelics are changes in perception, including different sensory modalities (i.e. visual, auditory, tactile) (Studerus et al., 2011; Schmid et al., 2015; Carhart-Harris et al., 2016), but also changes in the perception of time (Wittmann et al., 2007; Wackermann et al., 2008). Imagination is often reported to be highly vivid, and eyes-closed imagery of an "elementary" nature (i.e. colours and patterns) and of a "complex" nature (i.e. concrete objects, landscapes or entities) are both common (Carhart-Harris et al., 2011; Schmid et al., 2015; Studerus et al., 2011).

Cognitive- and behavioural experiments have demonstrated that impaired attention (Carter et al., 2005) and response inhibition (Quednow et al., 2012) after psilocybin, enhanced divergent thinking after ayahuasca (Kuypers et al., 2016), and increased spread of semantic activation under LSD (Family et al., 2016). Several studies have also assessed cognitive effects of psychedelics via self-report questionnaires, showing increased cognitive disorganisation (Carhart-Harris et al., 2016), disordered thinking (Studerus et al., 2011), muddled thinking (Carhart-Harris et al., 2011), and insightfulness (Carhart-Harris et al., 2016; Studerus et al., 2011, 2012).

In an effort to reconcile the "paradoxical" capacity of psychedelics to induce both "positive" effects (positive mood, enhanced creative thinking, insightfulness, etc.) and "negative" effects (impaired cognition, muddled thinking, etc.), these cognitive effects of psychedelics have been conceptualised as a modulatory effect on cognitive flexibility (Carhart-Harris et al., 2016; Carhart-Harris et al., 2014). Indirect support for the view that psychedelics enhance cognitive flexibility comes from a study that demonstrates psilocybin increases switching rate when attending ambiguous stimuli (Carter et al., 2007), and a study that demonstrated increased divergent thinking under ayahuasca (Kuypers et al., 2016).

The effects of psychedelics on emotion will be discussed separately in the following paragraph. Together, these studies illustrate the diverse spectrum of subjective effects psychedelics can occasion. This variety, was one of the motivations in the 1950s and 1960s, to try to exert some degree of control over the experience via, for example, utilizing non-drug variables. Some recent studies show support for this, demonstrating that acute drug effects can be predicted by several factors other than drug dose, including the mind-set of the individual, and the individual's personality traits (Studerus et al., 2012).

1.6.2 The effects of psychedelics on emotion and mood

The effect of psychedelics on emotionality was an important motivation to investigate their therapeutic potential, and modern studies have demonstrated that psychedelics increase emotionality via different research paradigms. Using mood rating scales, Hasler et al (2003) showed significant increases in "emotional excitability" under psilocybin (Hasler et al., 2003), and Schmidt et al (2015) demonstrated increases in "happiness" under LSD (Schmid et al., 2015). These findings were confirmed and corroborated by Dolder et al (2016) who compared two separate dosing regimens (100 mcg and 200 mcg of LSD) and reported a dose-response relationship for increases in emotional excitability (Dolder et al., 2016), confirming earlier observations of dose-dependency on emotionality (Studerus et al., 2011).

The study by Schmid et al (2015) also showed socio-emotional effects after LSD, such as increased closeness, trust and openness (Schmid et al., 2015). Dolder et al (2016) performed behavioural assessments targeting changes in socio-emotional information processing under LSD, and reported impaired recognition of fearful and sad faces, but enhanced emotional empathy (Dolder et al., 2016). Kometer et al (2012) reported a comparable emotional-information bias in a study showing that psilocybin produced a significant enhancement in positive mood and decreases accurate recognition of negative facial expression (Kometer et al., 2012). A study by Preller et al (2016) may be interpreted along similar lines, by showing reduced feelings of social pain under psilocybin within in a behavioural social exclusion task (Preller et al., 2016).

1.6.3 The effects of psychedelics on ego-functioning

As was detailed in the introduction chapter, one major reported effect of psychedelics is a temporary dissolving of boundaries between self (i.e. the "me") and object (i.e. the "not-me"). This effect has been referred to as disturbed ego-functioning, ego-disintegration or ego-dissolution, and was emphasised by many early researchers as an important underlying mechanism via which psychedelics may work therapeutically. It has recently been argued that, because of this effect, psychedelics represent an opportunity to study the mechanisms via which the human brain produces a coherent sense of self or ego (Carhart-Harris and Friston 2010; Lebedev et al., 2015).

Important for the present discussion is the study by Nour et al (2016), who demonstrated construct validity for ego-dissolution, and specificity of ego-dissolution for the experiences with psychedelics, over experiences with alcohol or cocaine (which were associated with the opposite effect, i.e. "ego-inflation") (Nour et al., 2016). Earlier questionnaire studies have also indicated prominent effects of psychedelics on ego-functioning, in particular via high ratings on the distinct ASC factor "oceanic boundlessness", defined as "positively experienced derealisation and depersonalisation" (Dittrich, 1998; Studerus et al., 2010), and via increased ratings for "impaired control and cognition" (Schmid et al., 2015), an important marker for disturbed ego-functioning. Finally, ego-dissolution has been related to enhanced suggestibility under LSD (Carhart-Harris et al., 2014) – an effect that has also been prominently hypothesised in early research as a potential therapeutic action of psychedelics.

1.6.4 The capacity of psychedelics to facilitate autobiographical experiences

The capacity of psychedelics to facilitate autobiographical experiences has not given much attention yet in modern research. Carhart-Harris et al (2011) demonstrated increased vividness for autobiographical memories (Carhart-Harris et al., 2012), and ratings in questionnaires that relate to autobiographical experiences, such as "I saw scenes from my past" are shown to be enhanced under psilocybin (Carhart-Harris et al., 2011)

1.6.5 The capacity of psychedelics to facilitate peak experiences

The capacity of psychedelics to facilitate peak experiences requires special attention, given the significant emphasis that was placed on its therapeutic value by early researchers in previous literature. Overall, pronounced subjective effects that are consistently reported include experiences of "blissful" emotions, a "sense of unity", and feelings of "spirituality" (Schmid et al., 2015; Studerus et al., 2011; Carhart-Harris et al., 2016), and these effects have been related to the ego-boundary dissolving effects of psychedelics (Nour et al., 2016). Although these studies suggest that psychedelics can produce subjective effects, that can be categorised under peak experiences, important work has been done by Griffith et al (2006, 2008, 2011), who explicitly studied the occurrence of peak experiences under psychedelics, and tested early hypothesis that these experiences are associated with sustained changes (up to months/years) in mood, behaviour and personality. The hallmark study of Griffith et al (2006) demonstrated that psilocybin is able to facilitate peak experiences (named by the authors as “mystical-type experiences”) with sustained personal meaning, in individuals who have never taken a psychedelic drug before (Griffiths et al., 2006). Subsequent studies replicated these findings and associated these experiences with enduring positive changes in outlook, personality and behaviour (Griffiths et al., 2008; Griffiths et al., 2011)

72% of the participants who received psilocybin for their first time reported the experience to be in their top 5 of most meaningful experiences in their lives, and 65% reported improved well-being 14 months afterwards. Maclean et al (2011) showed that only those individuals who experienced a strong, or “full” mystical-type experience, as defined by the Mystical Experience Questionnaire (MEQ), presented a significant increase in the personality trait “openness”, 14 months after the experience (MacLean et al., 2011).

These studies provide support for the hypothesis brought forth by earlier research that psychedelics can facilitate peak experiences, and support the view that peak experiences are associated with sustained positive changes. In addition, the studies showed that enduring positive changes can be instantiated by administering psilocybin only once or on a few occasions, and that these changes can occur in constructs, such as personality traits, that are normally considered stable in adulthood.

1.6.6 Clinical trials with psychedelics

In recent years, a number of clinical studies have focussed on the treatment of addiction- and mood disorders, and end-of-life care, using psychedelic therapy. Studies for psychedelic therapy for treating addiction have been implemented for tobacco-dependence and alcohol-dependence (Johnson et al., 2014; Bogenschutz et al., 2015). Johnson et al (2014) conducted an open-label pilot study to the efficacy of psilocybin-assisted psychotherapy for smoking cessation, and included 15 participants that had an average of six previous quitting attempts, and who smoked on average of 19 cigarettes per day for 31 years. The study showed that 12 of 15 participants (80%) completely abstained from smoking at a 6-month follow-up (Johnson et al., 2014), and 10 of 15 participants maintained abstinence at 12-month follow-up (Johnson et al., 2016). At the 12-month follow-up, 13 participants (86.7%) rated their experience with psilocybin to be “among the five most personally meaningful and spiritually significant experiences of their lives” (Johnson et al., 2016). Furthermore, the participants who rated high on measures for mystical-type experiences, personal meaning and spiritual significance, also showed the strongest sustained reductions in craving (Garcia-Romeu, Griffiths, and Johnson 2014), supporting the hypothesis that positive therapy outcomes are mediated by peak experience.

Bogenschutz et al (2015) performed the first open-label pilot study to test safety and efficacy of treating ten patients with alcohol-dependence with psilocybin (Bogenschutz et al., 2015). Patients showed a significant increase in drinking-abstinence following psilocybin, and these reductions were maintained at a 36-week follow-up. The general intensity of drug-effects during the psilocybin experience significantly predicted reductions in drinking and in craving 5 weeks later. Finally, Krebs and Johanson (2012) performed a meta-analysis on studies using LSD to treat alcoholism in the 1950s and 1960s, including six studies describing the treatment of 536 patients, and showed improvements up to 6 months after one dose of LSD (Krebs and Johansen 2012).

There are two open-label pilot studies that have assessed safety and efficacy of the use of psychedelics to treat major depression, one using the DMT-containing Amazonian plant-brew ayahuasca (Osório et al., 2015) and one using psilocybin (Carhart-Harris et al., 2016). Osorio et al (2015) administered ayahuasca to six patients with mild to severe depression and showed significant reductions in measures for depression up to 21 days after administration. Carhart-Harris et al (2016) administered psilocybin to patients with treatment resistant depression, who were in treatment on average of 18 years, and showed a 67% response rate (n=8) at 1 week after treatment with psilocybin, of which seven patients met the formal criteria for remission. Seven patients (58%) maintained their response for up to 3 months after the experience and five patients (42%) remained in full remission (Carhart-Harris et al., 2016).

Another application of psychedelic therapy concerns its use in end-of-life care, to improve quality of life in patients diagnosed with a terminal illness, by treating co-morbid diagnosis of anxiety-disorders and distress. Grob et al (2011) administered psilocybin to twelve subjects with advanced-stage cancer who had a diagnosis of acute stress or anxiety disorder due their illness (Grob et al., 2011). The study showed significant improvements in mood at 6 months' prior the experience, but the effect-size was small, nor did the outcomes correlate with measures for peak experiences (Grob et al., 2011). The authors argue that the findings may reflect the relative low dose that was used (0.2 mg/kg), compared with dosages used by Griffith et al (2006, 2008, 2011) (approx. 0.5mg/kg). Gasser et al (2014, 2015), provided two psychedelic therapy sessions with LSD to patients with end-of-life anxiety, and showed significant reductions in trait and state anxiety at the 2month and 12-month follow-up (Gasser et al., 2014; Gasser, Kirchner, and Passie 2015). The authors note, however that only 3 out of 8 patients in the experimental group, reduced anxiety-measures to a level below the diagnostic cut-off (Gasser et al., 2014). In a separate 12-month follow-up study, Gasser et al (2015) reported that 66.7% reported that LSD facilitated access to emotions, deepened introspection and insights, and changed personality and values. The authors note that the observed therapeutic changes were "mainly dependent on a related encompassing of emotional experiences" (Gasser et al., 2015). The most comprehensive studies towards the efficacy of psychedelic therapy in end-of-life care, are two recent double-blind placebo-controlled clinical trials (Griffiths et al., 2016; Ross et al., 2016). Griffiths et al (2016) showed acute improvements after high-dose sessions (30 mg/70 kg), with 80% of the 51 participants showing clinically significant decreases in depressed mood and anxiety at the 6-month follow-up (Griffiths et al., 2016). Ross et al (2016) demonstrated clinically significant reductions in depression or anxiety after one dose of psilocybin (0.3 mg/kg) that sustained in 60–80% of participants at the 6.5 month follow-up (Ross et al., 2016).

Finally, in a small open-label pilot-study, Moreno et al (2006) administered psilocybin to nine patients with obsessive compulsive disorder (OCD). Symptom severity was measured at baseline and at 4, 8 and 24 hours post-administration. All subjects demonstrated acute reductions in symptoms, ranging from 23% to 100% reduction. Compared to baseline, at 24-hours post-administration 88.9% maintained a reduction in symptoms equal or larger than 25%, and 66.7% maintained a reduction in symptoms equal or larger than 50% (Moreno et al., 2006). See appendix for study-details of these clinical trials.

1.6.7 Safety and efficacy of psychedelics

The results of these clinical studies show a promising prospect. Although the sample-sizes are small, the fact that remission and abstinence has been maintained for long periods after a single or a few sessions, is "unheard of" in psychiatry (Bogenschutz and Johnson, 2016). Particular notice must be given to the severity of the conditions of the patients in these studies, such as long-term drug-dependency (Johnson et al., 2015; Johnson et al., 2014) or treatment-resistance (Carhart-Harris et al., 2016).

Another important contribution of these pilot-studies is their demonstration of safety within patient populations. So far there are no adverse events reported, apart from temporary anxiety and thought confusion in some volunteers during the sessions. Needless to say, although the current data is suggesting a good safety-profile, the strict selection criteria and small study population sizes may have influenced these findings, and studies in larger populations are warranted. But the emerging picture suggests that psychedelics can be safely administered when appropriate guidelines are adhered. Indirect support for the safety-profile of psychedelics comes from meta-analyses that showed mental health complications following psychedelic drug use amongst users to be rare (i.e. <0.1%) (Cohen and Ditman, 1962). In addition, decreased rates of suicidality and psychological distress were reported among individuals with a history of psychedelic drug use (Hendricks et al., 2015) and there is no evidence for increased rates of mental health problems in populations who use psychedelics (Krebs and Johansen, 2013; Johansen and Krebs, 2015).

1.7 Neuroscience of psychedelics

To inform hypotheses and study-designs for the investigation of how psychedelics and music work in the brain in combination, an understanding of how they work separately is an important starting point. This section will provide an overview of early and modern neuroscience research of psychedelics. It will start with outlining the findings from neuroscience research with psychedelics at the microscopic level, i.e. the study of the interactions of psychedelics with neurotransmitter-systems in the brain, and then describe how this influences behaviour of neurons and their communication. This will serve as an introduction to the subsequent sections, which will review our current understanding on the effects of psychedelics on the macroscopic level, i.e. the changes produced by psychedelics in the behaviour of large populations or networks of neurons as measured by neuroimaging studies, and how these changes in brain function have been associated with some of the major psychological effects occasioned by psychedelics described previously.

1.7.1 Psychedelics act as serotonin 2A receptor agonists

Almost a decade after the discovery of LSD, the presence of the neurotransmitter serotonin was discovered in the human brain (Twarog and Page, 1953). It was the structural similarity between LSD and serotonin that made researchers speculate about a role of serotonin in producing the behavioural and subjective effects of LSD. First, experiments proposed contradicting mechanistic models, of LSD being either an antagonist (Gaddum and Hameed, 1954) or an agonist (Andén et al., 1968) on the serotonin receptor system. What aided the research significantly, was the increased knowledge on the different serotonin receptor subtypes (Peroutka and Snyder, 1979), and the development of selective serotonin antagonists. A series of studies using drug discrimination models in rats (Glennon et al., 1984) and primates (Li et al., 2008), showed that serotonin 2A antagonists, but not serotonin2C antagonists (Fiorella et al., 1995; Schreiber et al., 1994), blocked discriminative cues of psychedelics. Behavioural effects of psychedelics in mice, such as head twitching, have been successfully blocked by selective serotonin 2A antagonists and by knocking out genes encoding serotonin 2A receptors in mice (Halberstadt and Geyer, 2011; Halberstadt, 2015). Radioligand binding studies show a 10 to 100-fold higher affinity of LSD for the serotonin 2 receptor family, compared to other serotonin receptor sub-types (Titeler et al., 1988b), and serotonin 2A receptor affinity across different types of psychedelic drugs correlates with their potency (Glennon et al., 1984). However, ergotamide and lisuride do not produce behavioural or subjective effects like “classic” psychedelics such as LSD, yet they exhibit high serotonin 2A receptor affinity and agonist properties (Halberstadt and Geyer, 2010). This led to the identification of down-stream, intra-cellular signalling pathways that are recruited by psycho-active, but not by non-psychoactive serotonin2A agonists (González-Maeso et al., 2007).

Important evidence for the role of the serotonin 2A receptor in producing subjective effects of psychedelics was derived from human studies with serotonin 2A antagonists. Vollenweider et al (1998) showed that the effects of psilocybin are abolished when co-administered with the serotonin 2A receptor antagonists ketanserin and risperidone (Vollenweider et al., 1998). Subsequently, serotonin2A antagonists are shown to block effects of psilocybin within various cognitive- and behavioural measures, including tasks for automatic response inhibition (prepulse / sensorimotor gating) and controlled response inhibition (semantic / stroop interference) (Quednow et al., 2012), and experiments that assessed emotional biases and positive mood (Kometer et al., 2012). More recently, the effects of ayahuasca (Valle et al., 2016) and of LSD (Preller et al, 2017) were successfully blocked by ketanserin too. Together, these studies provide a body of evidence that indicates that psychedelics produce their subjective effects via activation of the serotonin 2A receptor.

1.7.2 Expression and activation of the serotonin 2A receptor

The serotonin 2A receptor is expressed throughout the neocortex, but is especially highly expressed in high-level association areas (defined in subsequent paragraph), including the posterior cingulate cortex, the anterior cingulate cortex, the medial temporal lobes and the insula (Erritzoe et al., 2010). What are the effects of activating these receptors? Upon activation of the serotonin 2A receptor, the neuron’s cell membrane depolarizes and becomes more excitable, i.e. more likely to fire in response to incoming action potentials (Andrade, 2011; Andrade and Weber, 2010). The outcome of this increased excitability depends on the type of neuron that is stimulated. The human neo-cortex is organised into distinct layers (six in total), and each layer is characterised by distinct cell types that are connected in a canonical fashion: distinct cell-types are forming a specific wiring-pattern, which is repeated, like the patterning of a tapestry, throughout the neo-cortex (Douglas and Martin, 2007). The majority of serotonin 2A receptors are expressed on excitatory glutamatergic pyramidal neurons within the deep layer V of the cortex, and to a lesser extent on GABA-ergic inhibitory interneurons (Celada et al., 2013). The deep layer V pyramidal neurons form an "output", projecting to hierarchically subordinate regions, whereas deep layer 5 inhibitory interneurons provide local inhibition of pyramidal neuronal activity (Bastos et al., 2012). The net-effect of increasing the excitability of both neuron-types may therefore be difficult to predict. Because interneuron-to-pyramidal-neuron communication orchestrates a meticulously balanced activation/deactivation of neuronal populations under normal conditions (Celada et al., 2013), one prediction is that increasing their excitability will have a desynchronizing or disordering effect on neuronal oscillations. The following sections will discuss the effects of serotonin 2A receptor activation on brain activity in more detail.

1.7.3 Human neuroimaging with psychedelics: Introduction

The micro-level organisation outlined above provides the elementary building-blocks for the macro-level organisation of the human brain - a highly complex network encompassing an approximate 100 billion neurons, that are organised into functionally segregated regions and networks of regions. Brains construct internal working models of their environment that motivate behaviours accordingly. Because this environment is ever-changing, and a critical source for survival as well as it is a continuous source of challenges and threads, much of the human brain evolved into highly specialized functions that account for the complexity and flexibility needed to thrive. Understanding *how* the brain does this, is the ultimate goal of human neuroscience. Neuroimaging, in turn, is one of human neuroscience's most valuable tools to do so.

Neuroimaging refers to the various techniques that allow the imaging of either the structural (anatomical) or functional (activity) characteristics of the nervous system. There are various modalities that allow the imaging of the living human brain, including electroencephalography (EEG), magnetoencephalography (MEG), direct recordings via implanted electrodes, positron emission tomography (PET), single photon emission tomography (SPECT), and magnetic resonance imaging (MRI). Each modality poses unique advantages and limitations, and in addition, the different experimental paradigms (e.g. the experimental scanning conditions) and the data-analyses techniques (i.e. the processing and drawing statistically-informed inferences from these measurements) add to the vast possibilities of how the human brain can be studied. An introduction into these paradigms, techniques and terminologies, and in particular those used in the research presented in this thesis, will be provided in the next chapter 2 (methodology). This section will focus primarily on providing an overview of human neuroimaging with psychedelics performed under resting state (task-free) conditions. These studies have produced important insights into how psychedelics change brain function, unconstrained by experimental conditions. Furthermore, these studies provide an important foundation from which to formulate the primary hypotheses in this study, that aim to understand how the way music is processed in the brain is changed under psychedelics.

1.7.4 Human neuroimaging with psychedelics: Early research

Reviewing early neuroimaging studies with LSD in the 1950s and 1960s presents a challenge, since both the technologies used and the methodological standards to statistically process and analyse complex time-series, have undergone significant advances over the last decades. Nevertheless, early studies that used direct depth EEG and scalp EEG to record spontaneous brain activity, have given important insights into possible brain mechanisms by which psychedelics may produce their subjective effects – of which some have been confirmed or indirectly supported by modern neuroimaging research.

One of the most consistent observations of the early work may be a lowering of the power or amplitude of spontaneous brain activity after psychedelics (Evarts, 1957). Decreases in the amplitude of spontaneous cortical activity are demonstrated after LSD and mescaline in rabbits (Delay et al., 1951; Rinaldi and Himwich, 1955), in cats (Bradley and Elkes, 1953; Bradley and Elkes, 1957), in rats (Macadar et al., 1970), and in humans (Bradley et al., 1953; Rinkel et al., 1952). Often these reductions in oscillatory power occurred in the alpha range and were accompanied by a simultaneous increase in the alpha frequency (Bradley et al., 1953; Rinkel et al., 1952). Schwarz et al (1956) performed a series of experiments utilising intracerebral recordings using depth EEG in patients with schizophrenia and convulsive disorders, and reported a “pronounced quieting effects” on brain activity, with simultaneous increases in infrequent recurrences of short bursts of “alpha-like discharges” in the visual cortex and deep in the temporal lobes (Schwarz et al., 1956). The authors reported that these sudden bursts of activity corresponded with the presence of eyes-closed visual hallucinations and the presence of music (Schwarz et al., 1956):

> “One patient had waxing and waning of the alpha-like spindles from the depths of the occipital region that corresponded with the rhythms of music. This appeared at the height of the mescaline effect but never appeared without music or in the control period with music”

The neuroimaging studies in this period led researchers to hypothesise an important role for the temporal lobe system in producing the subjective effects of psychedelics. Animal work described disorganised activity within the hippocampus (Macadar et al., 1970), and the disappearance of behavioural effects of LSD in chimpanzees whose temporal lobes have been removed (Baldwin et al., 1959). Monroe et al (1957) used depth electrodes to study the effects of LSD and mescaline on brain activity in humans, and associated disorganized activity within the hippocampus with the occurrences of visual hallucinations and emotionally charged memories (Monroe et al., 1957). Serafetinides et al (1965) corroborated these findings by demonstrating that after surgical removal of temporal lobes in humans with epilepsy, LSD lost its effectiveness in producing changes in amplitude or frequency of cortical activity (Serafetinides, 1965).

1.7.5 Human neuroimaging with psychedelics: Brain activity

Modern neuroimaging in animals is largely consistent with earlier work, showing pronounced reductions in oscillatory power across different frequency bands after administration of serotonin 2A agonists (Wood et al., 2012; Puig et al., 2010). In what follows, the aim is to provide a brief but comprehensive overview of the modern human neuroimaging research that has been done with psychedelics, with a focus on resting state neuroimaging paradigms.

The earliest modern EEG study with a psychedelic may be the report by Don et al (1998), who managed to perform field EEG recordings in participants of an ayahuasca ritual in Brazil. The study reported trend decreases in oscillatory power in the alpha and theta frequency bands, and trend increases in oscillatory power in the beta frequency bands (Don et al., 1998). Riba et al (2002, 2004) assessed the effects of ayahuasca on cortical activity using EGG in well-controlled experimental conditions, and confirmed earlier observations, showing broad-band power decreases in spontaneous brain activity after ayahuasca (Riba et al., 2002, 2004). Muthukumarawamy et al (2014) assessed the effects of psilocybin on resting state brain activity using MEG, and showed significant decreases in oscillatory power across frequency bands, with particularly pronounced decreases in the alpha frequency range. These decreases appeared localised in the posterior cingulate cortex, and the magnitude of the decreases in alpha activity correlated positively with ratings for ego-dissolution (Muthukumaraswamy et al., 2014). The finding that psychedelics decrease low-frequency oscillatory power in the human brain has since then been replicated with psilocybin (Kometer et al., 2015), LSD (Carhart-Harris et al., 2016) and ayahuasca (Schenberg et al., 2015). Carhart-Harris et al (2016) replicated previous findings with psilocybin, showing reductions in alpha oscillatory power within the PCC under LSD to correlate with ratings of ego-dissolution (Carhart-Harris et al., 2016). Kometer et al (2015) furthermore showed that decreases in oscillatory power under psilocybin extended into parahippocampal regions, which form part of the medial temporal lobe system (Kometer et al., 2015).

Previous studies measured effects of psychedelics on brain dynamics over one time-window during strongest drug effects. In contrast, Schenberg et al (2015) recorded resting-state cortical activity with EEG for over 2 hours in 25 minute intervals, and indicated that ayahuasca reduced alpha power 50 minutes post-administration, but that alpha oscillatory power was restored back to normal levels in subsequent measures at later time-points, and then accompanied by significant increases in gamma power (Schenberg et al., 2015).

Vollenweider et al (1997) reported increases in glucose metabolism in cortical and subcortical regions after psilocybin, including increases in the anterior cingulate cortex, the insula, the thalamus and the (medial and lateral) temporal lobes. These changes correlated with some of the subjective effects of psilocybin, such as visual hallucinations and ego dissolution, and in particular with increases in the cingulate cortex, medial temporal lobes and medial frontal lobes (Vollenweider et al., 1997). Similarly, Riba et al (2006) showed increased blood perfusion after ayahuasca in the anterior insula, the anterior cingulate, the left amygdala and parahippocampal gyrus (Riba et al., 2006). In contrast, the first fMRI study assessing acute effects of psilocybin by Carhart-Harris et al (2012), showed decreases in the BOLD signal and in cerebral blood flow (ASL) in cortical and subcortical regions, and these decreases appeared in high-level association regions such as the medial prefrontal cortex and the precuneus (part of the default mode network (DMN)), and correlated with subjective effects of psilocybin (Carhart-Harris et al., 2012). These findings have been replicated by Palhano Fontes et al (2015), who showed decreases in the BOLD signal after ayahuasca in DMN regions under resting state conditions (Palhano-Fontes et al., 2015). These findings have been interpreted as a disorganising or disintegrating effect of psychedelics on the integrity of high-level brain regions (Carhart-Harris et al., 2014). Accordingly, Tagliazucchi et al (2014) showed increased BOLD signal variability after psilocybin, with particularly pronounced changes within the hippocampi and the anterior cingulate cortex (Tagliazucchi et al., 2014). In accord with these findings, Lebedev et al (2015, 2016) showed that psilocybin and LSD produce significant increases in entropic brain activity, suggesting that brain activity becomes more dis-organised, unpredictable or uncertain (Lebedev et al., 2016; Lebedev et al., 2015).

1.7.6 Human neuroimaging with psychedelics: Brain connectivity

An important advancement in neuroimaging is the study of functional integration, i.e. the communication between anatomically and functionally segregated brain regions, and recent studies have provided insights into how psychedelics affect functional connectivity using fMRI. Carhart-Harris et al (2012) demonstrated significant decoupling between the medial prefrontal cortex and the posterior cingulate cortex (Carhart-Harris et al., 2012). This finding has since then been replicated with ayahuasca (Palhano-Fontes et al., 2015) and with LSD (Carhart-Harris et al., 2016). In addition, Lebedev et al (2015) showed a decoupling of the medial temporal lobe areas from parietal lobes after psilocybin (Lebedev et al., 2015), and Carhart-Harris et al (2016) showed decoupling of the parahippocampus (part of the medial temporal lobes) from the DMN after LSD (Carhart-Harris et al., 2016). The medial prefrontal cortex, the posterior cingulate cortex and the medial temporal lobes are structurally well-connected and show strong functional coupling under normal resting state conditions

(Raichle et al., 2001; Greicius et al., 2003). These regions are important high-level association regions that function like "communication hubs" - central nodes in a network that receive and integrate information from many disperse and different functionally specialised brain regions (Hagmann et al., 2008; Van den Heuvel et al., 2012). The pronounced reductions in functional connectivity between these regions facilitated by psychedelics suggests that a key mechanism via which psychedelics work in the brain is to dis-organise or dis-integrate the functional integrity of these high-level brain networks. This is in line with the body of evidence discussed previously indicating that psychedelics work by desynchronizing brain activity within high-level association cortices (Muthukumaraswamy et al., 2013; Carhart-Harris et al., 2016; Wood et al., 2012; Riba et al., 2002, 2004; Kometer et al., 2015).

In addition to studying changes of functional connectivity between different regions, valuable insights have emerged from studying changes in coupling between different brain networks. Two resting state brain networks that usually display anti-correlated or orthogonal activity, the DMN and the Task Positive Network (TPN), are shown to become positively coupled after psilocybin (Carhart-Harris et al., 2013) and after ayahuasca (Palhano-Fontes et al., 2015). Expanding on these findings, Roseman et al (2015) investigated thirteen separate resting state brain networks and reported marked increases after psilocybin between brain networks that are usually more strictly functionally segregated, in particularly for high-level association networks in which the serotonin 2A receptors are in highly expressed (Roseman et al., 2014), i.e. the posterior cingulate cortex and the anterior cingulate cortex within the DMN (Erritzoe et al., 2009). Similar findings were reported for LSD, including significant increased coupling between normally segregated brain networks, with simultaneous disintegrated activity within the networks themselves (Carhart-Harris et al., 2016). Tagliazucchi et al (2016) assessed the effects of LSD on whole-brain functional connectivity density (FCD), which corresponds to the strength of correlated activity for each region with all other parts of the brain, i.e. high FCD values indicate high global connectivity (Tagliazucchi et al., 2016). Key findings from this study are that FCD was increased within high-level association networks, such as the DMN and the salience network, and that FCD increases within the insula and the angular gyrus correlated with ego-dissolution (Tagliazucchi et al., 2016).

1.7.7 Neuroscience research with psychedelics: Summary

Taking these findings together, a picture emerges of psychedelics desynchronizing and disorganising neuronal activity via serotonin 2A receptor activation, and in particular within important hub-regions that form hierarchically high-level brain networks. Simultaneously, psychedelics facilitate an increased coupling between brain regions and networks that are normally more strictly functionally segregated. This "collapse" of the usual hierarchy of brain function, and the resulting decrease in the brain's modularity, may be a fundamental mechanism via which psychedelics produce their interesting subjective effects.

1.8 Neuroscience of music

One key question that this research aims to address is how psychedelics change the way music is processed in the brain. To the author's knowledge, there is only one reference in previous literature on the effects of psychedelics and music on brain function, and that is the study by Schwartz et al (1956) who reported that the effect of music under mescaline was associated with "alpha-like spindles", which "never appeared without music or in the control period with music" (Schwarz et al., 1956). A complete review of all neuroimaging research with music is beyond the present scope, but to formalise a working hypothesis, this section will provide an overview of the relevant studies that informed the present study's primary objectives: a discussion on the brain mechanisms of music-perception, music-evoked emotion, and music-evoked mental imagery.

1.8.1 Human neuroimaging of music-perception

Music is a highly dynamic and multi-dimensional stimulus, consisting of distinct acoustic features, such as pitch, loudness, tempo, rhythm and timbre. Accordingly, the neurobiological and cognitive processes involved in music-listening display a complex functional specialisation and a strong hierarchical organisation (Alluri et al., 2013; Toiviainen et al., 2014; Griffiths and Warren 2004; Koelsch and Siebel, 2005). This process serves the analysis of the spectral and temporal structures of the sound, and the linking of these patterns with high-level mental representations. Hereby, music attains its profound capacity to elicit thoughts, sensations and emotions (Koelsch 2010). One of the central insights of the neuroimaging of music-listening, is that music recruits large-scale brain networks involved in attention, working memory, episodic memory, motor function and emotion (Alluri et al., 2012). This has turned music into a valuable tool for cognitive neuroscience to study the functional organization of the human brain.

This processing of music starts at the lowest levels of the brain's hierarchy, at the cochlea, where incoming auditory information is filtered, before being forwarded to the brainstem and the medial geniculate nucleus (MGN) – a region within the thalamus that is specialised into relaying auditory information to the auditory cortex (Pannese et al., 2015; Pickles 2015). Within the auditory cortex, the processing of music starts by analysing music's "elementary" acoustic properties, such as the loudness, tempo, pitch and timbre. This process involves Heschl's gyrus, the superior temporal gyrus (STG) and the planum temporale, and these processes occur in parallel and are integrated progressively within the processing hierarchy (Kumar et al., 2007; Alluri et al., 2012; Griffiths and Warren 2004). The linking of acoustic information with complex "high-level" mental representations, is associated with information exchange between these auditory cortices and the inferior frontal gyrus (IFG). The IFG, also termed Broca's area, plays an important role in auditory working-memory, and has been implicated as a critical area for the syntactical processing of sound, that both music and spoken language have in common (Maess et al., 2001; Friederici et al., 2000; Koelsch 2006; Koelsch et al., 2002; Patel, 2003).

1.8.2 Human neuroimaging of music-evoked emotion

Music-evoked emotions are often described in the literature as "complex", since music not only evokes basic, "simple" emotions such as pleasure and fear, but often a mixture of emotions. Feelings of "nostalgia" or feelings of "wonder" are good example of such complex music-evoked emotion (Zentner et al., 2008; Juslin, 2013). The emotion-evoking effects of music are found to rely on the engagements of both limbic brain areas, such as the amygdala and the striatal system (Blood and Zatorre 2001; Blood et al., 1999; Salimpoor et al., 2011), and high-level association cortices, such as the insula the hippocampus and the orbitofrontal cortex (Petrini et al., 2011; Koelsch 2014; Trost et al., 2012).

The ventral striatum is consistently activated to music, and several neuroimaging studies have associated the ventral striatum with music-evoked pleasure and the encoding of music-evoked reward (Salimpoor et al., 2009, 2011). Of particular significance for the present study may be the notably high numbers of studies that implicate an important function of the medial temporal lobe system (including hippocampus and parahippocampus) and the insula in music-evoked emotion (Koelsch 2014; Frühholz et al., 2014). The medial temporal lobes are high-level unimodal association cortices, specialised in memory-formation, memory-activation and context-dependent cognition (Lavenex and Amaral, 2000), and are considered to be important for top-down regulation of emotion (Pessoa, 2017). In turn, the insula is often activated to music-evoked emotion, and has been more described as a high-level association region involved in self-awareness and emotional –awareness (Craig 2009; Gu et al., 2013; Singer et al., 2009).

1.8.3 Human neuroimaging of music-evoked mental imagery

Mental imagery is defined as a perceptual experience, without the presence of an external perceptual stimuli (Arbuthnott et al., 2001; Abraham, 2016). Neuroimaging studies suggest that mental imagery has overlapping, if not identical, neural mechanisms to the neural mechanisms underlying perception (Kosslyn et al., 2001). With regard to the relationship between music and mental imagery, musical mental imagery has been studied in the context of music performance (Aleman et al., 2000; Keller, 2012), but there exists a significant lack of knowledge into how music can evoke visual mental imagery. This is striking, since music's effect on mental imagery, and more broadly on spontaneous imagination, is popularly considered to be amongst music's major effects, and plays a central role in several music therapy modalities (Schulberg, 1999; Summer, 2011; Finch and Moscovitch, 2016).

1.9 Primary research objectives of this thesis

This introduction chapter provided an overview of the historical and modern scientific knowledge and psychotherapeutic perspectives on psychedelics and music. It highlighted how music plays a central role in the increasing numbers of clinical trials that implement and study psychedelic therapy, yet it demonstrated how little is known empirically on the function of music in this context. The reportedly profound effects of psychedelics on the subjective experience of music suggests that music may play an important therapeutic function, that demands empirical studies in order to advance the rapidly expanding scientific and psychotherapeutic community that works with psychedelics and music in combination. Furthermore, by studying the brain mechanisms underlying their combined effects on subjective experience, our understanding of how the brain processes music and complex subjective states may be significantly furthered. Example of this are the brain mechanisms underlying complex emotions associated with peak experiences, autobiographical experiences and visual mental imagery evoked by music.

The primary research objectives of this thesis are (1) to study the acute effects of psychedelics and music in combination on brain function under LSD (2) to associate changes in music-evoked emotion and music-evoked mental imagery with changes in brain function under LSD, (3) to study the music-experience in psychedelic therapy with psilocybin and the relationship between music-experience and therapy outcomes. These objectives will be addressed via four separate studies, of which the hypothesis and methods will be discussed separately in more detail in each corresponding chapter:

Study 1: Effects of LSD on music-evoked emotion

Objective: To study changes in music-evoked emotions under LSD in healthy volunteers.

Study 2: Effects of LSD and music on brain activity and emotion

Objective: To investigate changes in music-evoked brain activity and music-evoked emotion under LSD, using fMRI in healthy volunteers.

Study 3: Effects of LSD and music on parahippocampus connectivity and mental imagery

Objective: To investigate the neural correlates of music-induced mental imagery under LSD, using fMRI in healthy volunteers.

Study 4: Music-experience in psychedelic therapy

Objective: To assess the phenomenology of the music-experience in patients with depression undergoing psychedelic therapy with psilocybin, and the relation between music-experience and therapy outcomes.

"The conclusion from all these considerations is that the most important step in the art of being, is everything that leads to and enhances our capacity for heightened awareness and, as far as the mind is concerned, for critical, questioning thinking"

Erich Fromm

2 Methodology

This chapter serves to provide an introduction into the methods used in this research. It will briefly explain the background of functional magnetic resonance imaging (fMRI), and introduce the different fMRI data analysis methods used to measure changes in brain function (BOLD activity, functional connectivity and effective connectivity). Finally, it will introduce the selection of the psychological metrics used to study changes in musical experiences under LSD, including the Geneva Emotional Music Scale (GEMS) and Interpretative Phenomenological Analysis (IPA). The chapter will outline the study-designs that were used in the experiments in this thesis, but details will be provided seperatey for each separate experiment in the corresponding chapters.

2.1 A brief introduction to fMRI research

The emergence of fMRI in neuroscience research in the 1990s had a revolutionary impact in the field. It was the first time that neuroscientists were able to measure human brain activity non-invasively and *in vivo* in a relative high spatial resolution. MRI works by exploiting the behaviour of hydrogen (H) atoms in a strong magnetic field. The MRI machine applies a strong magnetic field, that aligns the hydrogen protons with the magnetic field. Subsequently, radio frequency energy is applied to the hydrogen protons in the brain using a gradient coil around the head, "exciting" the protons into a high-energy state and "flipping" the protons 90° from the magnetic field axis. After excitation, the hydrogen protons release radio frequency energy while returning to their "relaxed" baseline state. This release of radio frequency energy is measured by the MRI scanner, and underlies the generation of an image. The full 3D brain images are usually acquired one slice at a time, with each slice being a 2D image. To overcome this relatively slow process, gradient echo planar imaging (EPI) techniques were developed that allow a faster acquisition of sequences of images, by collecting multiple "echoes" from each radio frequency pulse, providing one full brain image each few seconds - depending on the MRI scanner & selected parameters.

fMRI measures the blood oxygenation level-dependent (BOLD) signal, which is a surrogate or indirect signal for brain-activity. The BOLD signal reflects the oxygenation of blood in the brain, estimated via magnetization difference between oxyhaemoglobin and deoxyhaemoglobin. When brain areas have increased synaptic brain activity, these areas undergo an increased metabolic demand, which results in the proportion of oxyheamoglobin and deoxyhaemoglobin to be relatively reduced. Thus, the BOLD-signal correlates with brain activity, and hence, BOLD-increases are typically inferred as increases.

There are several limitations using fMRI to study changes in brain function. One major limitation of measuring the BOLD signal, is that the signal changes occur much slower than real brain activity (up to 80Hz). Changes in blood flow show a slow peak (5 second from the beginning of the increase), a signal referred to as the haemodynamic response function (HRF), and thereby significantly limit the temporal resolution of the BOLD measure. Secondly, the BOLD-signal changes are non-absolute, making only relative fluctuations in BOLD signal within one scanning session utilisable. Thirdly, the analyses of the BOLD-signal need to take into account a significant amount of noise in the data (e.g. non-specific background noise or head-movement artefacts in the measured fMRI signal). And finally, one needs to be reminded, that despite the superior spatial resolution of fMRI when compared with other neuroimaging modalities, the BOLD-signal that is measured per 3-dimensional unit or voxel, still represents the mixed activity of approximately one million neurons (Arthurs and Boniface, 2002; Logothetis, 2008; Logothetis and Wandell, 2004).

Nevertheless, advances in methodology have made fMRI a dominant paradigm for relating brain function to behaviour and cognition, and over the previous decennia, fMRI has provided important insights into the brain's functional organisation. For example, fMRI research has highlighted the functional specialisation of functionally segregated "modules" that are localised in distinct regions and networks of the brain, such as for example the auditory cortex being specialised into the processing of auditory information (Morosan et al., 2001; Hackett, 2011). Furthermore, fMRI research furthered our understanding of the functional organisation of the brain, and highlighted processing hierarchies. For example, auditory information received by the cochlea, is forwarded to areas in the brain stem and the thalamus that are specialised into the processing of sound, which then relays this information to the primary auditory cortex in ascending levels of specialisation, abstraction, and association (Hackett 2011; Kumar et al., 2007; Romanski et al., 1999; Wessinger et al., 2001). The auditory cortices, in turn, represent different regions specialised into processing different properties of the sound, including its pitch, loudness and timbre. This will then be forwarded, in parallel, to other areas that process the *what* (object recognition) and the *where (localisation)* of the sound, and link the sound with complex mental representations and emotional responses (Wang et al., 2008; Bizley and Cohen, 2013; Romanski et al., 1999; Hackett 2011). The further in the processing hierarchy, the more abstracted and multi-modal the signal is processed. This is one example of how fMRI research has advanced the field, by moving the focus away from localising specialised brain functions, to studying how brain areas communicate with each other as part of a highly interconnected complex system of processing units - also known as *functional integration* (Friston, 2011). Understanding how the brain coordinates and integrates activity from separate specialised regions as a dynamic network, is one of the central challenges in neuroscience research today. The experimental methods representing these advances that were used in this research, will be the focus of the following sections.

2.2 Methods for fMRI research

2.2.1 Designing fMRI experiments

The hypotheses that fMRI allows to address are determined by the design of the experiment. A general distinction can be made between stimulus- or task-based paradigms and resting-state or task-free paradigms. In a task-based paradigm, the aim to is to present a stimulus or a cognitive/behavioural task for a certain duration (a block or epoch) (e.g. an auditory tone for 5 seconds), and to contrast this with a control condition (e.g. silence for 5 seconds). Contrasting these two conditions will then allow to identify the brain regions that are more activated (sound > silence) or less activated (silence > sound) during the auditory tone. Task-based paradigms, allow to investigate specific modes of perception and cognition (e.g. auditory processing and working memory). In contrast, task-free or resting-state paradigms are characterised by the absence of stimuli or tasks, and allow to investigate “resting-state” brain functioning, and the “spontaneous” cognition associated with this (e.g. self-referential thinking or day-dreaming). A baseline or “default mode” of resting brain function was discovered via observing consistent de-activations in a set of brain regions during tasks (Raichle et al., 2001). This led to identification of resting state brain networks, and to important insights into the intrinsic functional organisation of the human brain (Fox et al., 2005; Greicius et al., 2003; Yeo et al., 2011).

With regard to the fMRI experiments (study 2 and 3), the stimuli consisted of full music tracks, that were contrasted with a stimulus-free condition (resting-state) to study an effect of music. In addition, given the objective to assess how psychedelics alter the effects of music on the brain, the experiments consisted of two separate study days, where on one day placebo (saline) was administered, and on the other day the drug (LSD) resulting in a factorial design (i.e. two conditions (music vs no music), present within 2 conditons (LSD vs placebo). The order of the conditions was randomised, to control for possible order-effects. These criteria did not apply to study 1, which was placebo-controlled, but in fixed order, and study 2, wich was an open-label clinical trial (i.e. with no placebo condition). Detailed motivations behind these study designs, including the motivations behind the music selection, are provided in the respective chapters.

2.2.2 fMRI scanning and data pre-processing of fMRI data

Neuroimaging was performed on a 3T GE HDx system. An initial 3D FSPGR anatomical scan was obtained in an axial orientation, with field of view = 256× 256× 192 and matrix = 256 × 256× 192 to yield 1-mm isotropic voxel resolution (TR/TE = 7.9/3.0 ms; inversion time = 450 ms; flip angle = 20°). This was used for registration and segmentation of functional images. Functional images were acquired using a gradient echo planer imaging sequence, TR/TE = 2000/35ms, field-of-view = 220mm, 64 × 64 acquisition matrix, parallel acceleration factor = 2, 90° flip angle. 35 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 BOLD scans was 7 minutes and 20 seconds.

fMRI scanning sessions usually acquire a high-resolution anatomical/structural (T1-weighted) image and a number of functional (T2-weighted) images. Both the structural and functional images undergo a sequence of pre-processing procedures. This is critical, in order to correct for motion- or scanner- related noise in the data and to be able to compare the functional scans across subjects. The methods used in this thesis aimed to reflect the most recent advances in pre-processing methods (such as for example methods for correcting for motion-artefacts), in accord with the significant changes these guidelines underwent over recent years.

The fMRI pre-processing programme was assembled from several different complementary imaging software packages: FMRIB Software Library (FSL) (Smith et al., 2004), AFNI (Cox, 1996), Freesurfer (Dale et al., 1999) and Advanced Normalization Tools (ANTS) (Avants et al., 2011) were used. More details of the utilised pre-processing procedures and the chosen parameters are provided in the methods section of each separate neuroimaging study (study 2 and 3), but in general, the following pre-processing procedures were included:

1) De-spiking (3dDespike, AFNI): removal of “spikes” in the time series, to correct for motion artefacts.

2) Re-allignment (3dvolreg, AFNI): registration (mapping) of each functional image to the functional image that is most similar to all other images within the same scanning session (per subject), to correct for motion artefacts.

3) Brain extraction (BET, FSL): removing of all non-brain tissue from the structural images, to aid subsequent image registration of functional images onto anatomical images.

4) Anatomical registration (rigid body registration using FSL’s BBR, or Freesurfer’s *bbregister* when done manually): registration of all functional images to anatomical image per subject.

5) Template registration (aka normalisation) (SyN), ANTS): Non-linear registration to 2mm MNI template brain to align all subject-level images to the same *template* image, allowing subsequent group level analyses.

6) Scrubbing (Power et al., 2012): substituting TR’s with high framewise displacement (FD), to correct for motion correction.

7) Spatial smoothing (FWHM) (3dBlurInMask, AFNI): convolution of the BOLD signal with a 5mm full-width gaussian kernel, to control for spatial inhomogeneity and for radio frequency noise within the scanner .

8) Temporal filtering: using a high-pass filtering at a cut-off frequency of 0.01 Hz to remove baseline signal drifts in the BOLD signal, to correct for scanner noise (drift) correction.

9) Nuisance regressors (9 in total) were added into subsequent data-analysis (General Linear Model, explained below) to correct for motion correction. These were six motion-related (3 translations, 3 rotations) and three anatomically-related (not smoothed).

2.2.3 The General Linear Model

The general linear model (GLM) is a statistical linear model, consisting of explanatory variables that predict the response variable. In fMRI data analysis, the GLM typically implies a multiple linear regression, where the BOLD signal is the response variable (Y), described by a linear combination of multiple explanatory variables (X), which can be the time courses that describe the experimental design (e.g. presence or absence of auditory tone) and nuisance- or noise-variables (e.g. time courses for head-movement). This is written as:

$$Y = \beta_0 + X_1\beta_1 + X_2\beta_2 + \ldots + \varepsilon$$

For each voxel, the GLM finds the weights (β_i) that minimize the residual variance (ε) between the predicted and observed BOLD signal. This informs a statistical map for explanatory variables of interest, that can be examined in isolation or can be contrasted with other variables (e.g. auditory tone A versus auditory tone B). This statistical map illustrates BOLD-activations or BOLD-deactivations on a subject level, but most fMRI studies aim to make inferences on group level (e.g. condition A compared to condition B). To do so, the estimates of the subject-level GLMs enter a group-level (high-level) analysis, which typically involves a t-test or ANOVA. This results in a group average, which can be contrasted between different conditions (e.g. LSD vs placebo).

2.2.4 Measuring changes in BOLD activation

The analysis employed in study 2 (chapter 4), will assess BOLD activity changes related to different aspects (acoustic features) of the music. This study follows a classical task-based design as described above, where multiple time courses, each describing a distinct feature in the music, will be added as regressors into one GLM (e.g. loudness, pitch, brightness, etc.).

This allows the generation of a statistical map for each different acoustic feature, and thereby allows to assess what regions are involved in the processing each separate feature, and subsequently, to investigate the differences between drug and non-drug condition in processing these features.

2.2.5 Measuring functional integration: Functional connectivity

As was said in the beginning of this chapter, the field has witnessed a significant shift in focus from studying functional localisation to studying functional integration. Various ways of assessing functional integration in the human brain have been developed for analyses of fMRI data (Friston, 2011; O'Reilly et al., 2012). The most commonly employed are measures of "functional connectivity", which refers to the statistical dependencies, or correlations, between time courses representing BOLD-signal variations from different voxels or regions. In the present study, functional connectivity has been measured by using "seed-based paradigms", where the BOLD signal time-course of one region of interest (ROI, the "seed") is extracted to correlate against each other voxel in the brain. The research presented here used two different seed-based methods of measuring functional connectivity:

Standard seed-based functional connectivity: In seed-based functional connectivity analyses, the BOLD-signal timecourse from one region of interest (ROI), i.e. the "seed", is extracted and correlated against each other voxel in the brain. This allows the identification of other regions that show co-variation in activity with the seed region, and permits to assess the changes regions or networks of regions show in correlated activity, across different experimental conditions (e.g. comparing functional connectivity between LSD and placebo conditions) (Friston, 2011).

Psycho-physiological interaction analysis: In psychophysiological interactions (PPIs) analyses, a time course from one seed ROI is extracted, and then multiplied, element-by-element, with the task-regressor. This generates a "PPI regressor", that will correlate with the seed ROI time course during tasks, but anti-correlated with the seed ROI time-course during rest blocks. Therefore, when the PPI regressor is correlated against each voxel in the brain, task-specific changes in functional connectivity can be revealed (O'Reilly et al., 2012).

2.2.6 Measuring functional integration: Effective connectivity

Correlations can however arise in various ways. For example, activity in two separate regions can correlate because they share a common input of the stimulus, or their activity correlates because activity in one region causes activity in another via excitatory forward connections. Measures for the latter are called "effective connectivity", i.e. the causal or *directed* information flow between separate brain regions (Friston, 2011). Measures for effective connectivity take into account the hierarchical organisation of the brain via differentiating between forward and backward connections, and hence give a more accurate depiction of the involved brain mechanisms. Effective connectivity can be assessed by different methods, including Granger Causality, Structural Equation Modelling and Dynamic Causal Modelling (DCM). In the present study, effective connectivity was assessed using DCM. Informed by standard DCM procedures, this was preceded by functional connectivity analyses to identify the network to interrogate with further hypothesis testing using DCM (Friston et al., 2003; Karl J. Friston et al., 2011; B. Li et al., 2011; Stephan et al., 2010).

Dynamic causal modelling: DCM is a biologically-informed modelling procedure that estimates the causal interactions (i.e. effective connectivity) between different pre-selected nodes of a network, and the changes in coupling strength between and within those nodes (extrinsic and intrinsic connections respectively) due to experimental manipulations. The basic architecture of a model is defined by structurally plausible and functionally-informed brain regions, whose connections are defined as either bilinear (i.e. information flow between regions) or non-linear (i.e. activity in one region modulating information flow between regions). Typically, experimental manipulations can directly affect activity in each node (as 'driving inputs') or alter the strength of coupling within or between nodes (as 'modulatory inputs') (Friston et al., 2003).

In DCM, a series of plausible models, representing competing hypotheses, are specified. Each model corresponds to a hypothesis about how observed changes in BOLD signal were caused by changes in neural activity in each network node. The different models can vary in terms of the position of driving and modulatory inputs. DCM uses a biophysical model of the hemodynamic response to predict the underling neuronal activity – and the underlying (changes in) connectivity – from the observed BOLD signal. Model estimation, or inversion, returns conditional estimates for the changes in connectivity and scores the model in terms of its accuracy and complexity (Kahan and Foltynie, 2013; Friston and Penny, 2011; Stephan et al., 2010).

Following model estimation, Bayesian Model Selection (BMS) is used to compare different models to identify the model with the greatest evidence – i.e. the model that offers the best explanation of the data. This model can be selected to assess coupling parameters post-hoc, to characterize the size and direction of the changes in connection strength caused by the experimental manipulations. Coupling parameters quantify the strength of the coupling in terms of the rate (in Hz) at which a response is caused in a given region, and modulation is expressed as either an increase or decrease in this coupling measure (Friston, 2003; Friston and Penny, 2011; Kahan and Foltynie, 2013).

2.3 Methods for qualitative research

This thesis also aims to investigate changes in the subjective experience of music under a psychedelic. In particular, the objective is to assess changes in music-evoked emotion and music-induced imagery, to associate these effects with measured changes in brain function in the neuroimaging studies, and to study the music-experience during psychedelic therapy. The methods employed to do so, include questionnaires, visual analogue scales (VAS) and qualitative analysis of interview data.

Visual Analogue Scales and questionnaires: Visual analogue scales (VAS) for questions that assess the subjective experience of music were implemented. Examples of such questions are “how emotionally affected were you by the music?” (study 1), or “did you experience simple eyes-closed imagery?” (study 2), and responses to these questions are scored on a VAS scale ranging from 0 to 100, with respective anchors to indicate the qualitative meaning of the value. Comparing average ratings between conditions, allows to assess difference in subjective experience between drug and non-drug states, and the change-scores (drug>non-drug) allows correlation-analyses that associate changes in subjective experience with changes in brain function (e.g. correlating increases in ratings for mental imagery versus changes in effective connectivity (study 3)).

There have been several psychological metrics developed to assess music-evoked emotion. A classic approach utilises a 2-dimensional model that differentiates between arousal (activating versus relaxing), and valence (positive emotions versus negative emotions). The critique on this metric is that it does not acknowledge the complexity inherent in music-evoked emotion: music-evoked emotions are argued to often be a mixture of *basic* emotions. For example, feelings of nostalgia include feelings of sadness (negative valence) and joy (positive valence) (Juslin, 2013; Zentner et al., 2008). Some argued that those complex or *aesthetic* emotions are what makes the scientific study of music-evoked emotions in particular significant, and questionnaires have been developed that address this, such as the Geneva Emotional Music Scale (GEMS). This study uses the GEMS, which has been derived from a sequence of studies, starting with qualitative studies, towards large-sample rating studies, that used factor-analyses to validate distinct dimensions or factors of music-evoked emotion (Zentner et al., 2008).

Phenomenological analysis. The objective of study 4 was to deepen our understanding of the subjective experience and therapeutic function of music in psychedelic-assisted psychotherapy. Understanding patient-experiences in a naturalistic setting was an important motivation for this objective, given other expriments in this thesis concerned effects of psychedelics and music on healthy voltuneers, and within a context that is strikingly different from the therapeutic application (i.e. fMRI scanner vs quiet room with supportive therapists and music listening).

To accomplish this objective, like in any other experiment, the study design determines the the conclusions that can be drawn. Science, in simplest terms, is a practice of advancing an emperical understanding of reality by finding meaningful patterns in data, in order to, in the words of physicist David Deutsch, "test new theories that seem to show promise of explaining things better than the prevailing ones do" (Deutsch, 1997).

To find meaningful patterns, many research designs are hypotesis-driven, in which the experiments are designed as such so that inferences can be made regarding specific, isolated variables of interest. A caveat with hypothesis-driven approaches is that hypohteses are per definition bounded by the limitations of current knowledge (Helden, 2013). Designing experiments with prior expectations, therefore, runs the risk of biasing and thereby excluding alternative, better explanations. This is especially problematic, when chartering unknown terrorities, such as the case in this thesis. Data-driven research approaches, on the other hand, allowing inferences to be told by the "data itself" (Shih, 2016), on the assumption that when prior beliefs are absent there is a greater possibility of insight into a phenomenon "where nobody had looked before" (Helden, 2013).

For study 4, we haven implemented a qualitative (semi) data-driven approach, called interpretative phenomenological analysis (IPA) (Smith et al., 1997). This approach was chosen to analyse interviews with patients about their experience with the music during psychedelic therapy psilocybin, after their therapy session. The interviews consisted of open questions (for example: "Did the music influence your experience? And if so: in what ways?", to allow patients to share, using their own words and interpretations, unbiased by the researcher's hypotheses, *whether or not*, and *how* the music influenced their subjective experience. IPA is an approach increasingly used in healthcare research (Biggerstaff and Thompson, 2008; Smith, 2011), and is considered in particular appropriate when ascertaining and unveiling the complexity behind patients' subjective experiences (Smith, 2011). Details on the methods and implementation of this analysis will be provided in the corresponding chapter (Chapter 6).

2.4 Overview of software used for data-analyses

FSL FEAT GLM was used in experiment 2 to assess effects of LSD and music on BOLD activation. Statistical Parametric Mapping (SPM12b) was used for GLM and DCM analyses in experiment 3. The Music Information Retrieval (MIR) toolbox (version 1.6.1) (Lartillot and Toiviainen, 2007), implemented in MATLAB, was used to extract acoustic properties in the music in experiment 2. MATLAB was used to extract timecourses from ROI's. And all other statistical tests (t-tests, Anova's and correlation analyses) were performed in Statistical Package for the Social Sciences (SPSS) for Windows. (For overview of software used for pre-processing of fMRI sata see 2.2.2)

2.5 Study approvals

All studies were approved by the National Research Ethics Service (NRES) London and by Imperial College London's Joint Research and Compliance Office (JRCO) West London and was conducted in accordance with the revised declaration of Helsinki (2000), the International Committee on Harmonisation Good Clinical Practice guidelines and NHS Research Governance Framework. Imperial College London sponsored the research which were conducted under a Home Office license for research with schedule 1 drugs. The National Institute for Health Research/Wellcome Trust Imperial Clinical Research Facility provided approval for the study-site for study 4.

"For me, the climax of the service came during a solo that was sung by a soprano whose voice (as it came to me through the prism of psilocybin) I can only describe as angelic. What she sang was no more than a simple hymn, but it entered my soul so deeply that its opening and closing verses have stayed with me ever since … "*My times are in Thy hands my God*" … the gestalt transformed a routine musical progression into the most powerful cosmic homecoming I have ever experienced"

Huston Smith

3 *Study 1* | Effects of LSD on music-evoked emotion

3.1 Background

The rather profound effects of classic psychedelics on emotion that early researchers in the 1950s and 1960s observed, was one of the primary motivations for their therapeutic use. It was believed that by dismantling usual control-mechanisms, or "ego defences", psychedelics enhance emotional therapeutic processes (Busch and Johnson, 1950; Kurland et al., 1971). Like was detailed in the introduction chapter, psychedelics were found to produce a diverse spectrum of subjective experience, and music was introduced as a means to promote the occurrence of those types of experiences that were believed to have most therapeutic significance. These included peak experiences as well as autobiographical experiences (Bonny and Pahnke 1972; Grof, 1980). Music became a key component in psychedelic therapy sessions, and is still used in modern psychedelic therapy studies (Griffiths et al., 2016; Ross et al., 2016; Grob et al., 2011; Gasser et al., 2014; Carhart-Harris et al., 2016; Bogenschutz et al., 2015; Johnson et al., 2014).

Psychedelics under music-listening conditions are shown to reliably facilitate peak experiences (Griffiths et al., 2006), and those experiences are correlated with sustained positive changes in behaviour (Griffiths et al., 2008), personality (MacLean et al., 2011), and clinical outcomes (Griffiths et al., 2016; Ross et al., 2016; Johnson et al., 2014). To study the contribution of music in facilitating these types of experiences, a basic question must first be addressed: *is music-evoked emotion intensified under psychedelics?*

This first study sought to test the hypothesis that music-evoked emotion is enhanced under the classic psychedelic drug LSD. Secondly, to probe more specific aspects of participants' emotional experiences during music listening, the Geneva Emotional Music Scale (GEMS-9) was implemented (Zentner et al., 2008). The GEMS was developed to measure a range of emotional experiences during music listening and has been considered in particular useful to assess complex or “aesthetic” emotions, such as feelings of “transcendence”, “wonder” and “nostalgia”. The study predicted that the emotional response to music is higher under LSD, and that specifically emotions related to peak experiences (“transcendence” and “wonder” (Maslow 1964, 1971)) would be enhanced.

3.2 Methods

3.2.2 Recruitment and screening of participants

All study participants were recruited via word of mouth and gave written informed consent before participating in the study. Prior to study enrolment, all participants were screened in a clinical research centre at the Hammersmith hospital campus of Imperial College London (the Wellcome Trust Clinical Research Facility, WTCRF). This screening consisted of recording of demographic information and medical history, as well as a physical examination (electrocardiogram (ECG), routine blood tests and blood pressure measurement), and a psychiatric assessment. All participants gave full disclosure of their drug taking histories. Participants and were properly briefed on the study and the potential drug effects.

Key exclusion criteria were: <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 (E.g. LSD, mescaline, psilocybin/magic mushrooms or DMT/ayahuasca), having experienced a persistent adverse reaction after psychedelic drug use, pregnancy, problematic alcohol use (i.e. > 40 units consumed per week), or a medically significant condition rendering the volunteer unsuitable for the study.

3.2.3 Drug dosing and setting

One thousand µg of LSD freebase (certified 99.4% purity) was reconstituted with 10ml saline and sterile filtered, yielding a 100µg:1ml sterile solution. Since a primary motivation of the study was to determine a safe and appropriate dose of LSD for a subsequent neuroimaging study, the dosage of LSD varied among participants, i.e. one received 40µg, two 50µg, six 70µg and one 80µg. For each administration, the appropriate amount of LSD solution (E.g.

0.7ml = 70µg) was transferred to a 10ml syringe and made up to 10ml with saline. The 10ml solution was then infused intravenously over a three-minute period, followed by a 60 second infusion (“flush”) with 10ml saline.

The experiments were performed at the WTCRF at the Hammersmith Hospital. All experiments took place in a clinical room, consisting of a hospital bed, physiological monitoring equipment and *en suite* bathroom facilities. Since psychedelics have the potential to induce psychological distress, the clinical conditions of the room were adapted to promote feelings of comfort and safety, i.e. the lighting was dimmed and the room was decorated with soft furnishings (Johnson et al., 2008). The setting was identical for all study days.

3.2.4 Experiment overview and procedures

Participants were carefully prepared for the drug experience at screening and the study was conducted in accordance with guidelines for the safe management of psychedelic drug sessions (Johnson et al., 2008). This included psychoeducation on the subjective effects of LSD, introductions to the research-team that will be present, and an outline on how the experiment days are structured. After screening, eligible participants attended two study days, with at least five days in between. Participants were told they would receive LSD on one of these two occasions but were not told in which order. Thus, participants were blind to the condition (i.e. drug or placebo), however the researchers were not. Placebo (10ml saline) was always administered on the first day. This single-lind fixed order design was chosen to 1) avoid potential carry-over effects (E.g. residual psychological effects) of LSD into the next session, given evidence psychedelics can occasion changes in berhaviour and persionality up to months after the experience (Maclean et al., 2011), and also 2) given experiences with psychedelics can be profound, having the placebo session first was argued to build inter-personal rapport, prior the drug session. Aware of the trade-offs of this design choice, the limitations are acknowledged and discussed in the discussion section.

Volunteers arrived at the research centre between 10:00am and 11:00am on testing days, were briefed about the study procedure, gave a urine test for drugs of abuse and pregnancy (where relevant) 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. Subsequently, volunteers were encouraged to close their eyes and relax in a reclined position before a 10ml solution of saline alone (placebo) or containing LSD was intravenously infused over a period of 3 minutes. Blood pressure was measured prior to dosing (baseline), 45 minutes after dosing and at the end of the study day (prior to discharge). Heart-rate was recorded at regular intervals, together with self-ratings of the subjective intensity of the drug effects on a scale of zero ("no effects") to ten ("extremely intense effects"). These measurements were taken every 1-5 minutes during the first 45 minutes post-infusion, and then continued in intervals of approximately 30-45 minutes until the end of the experiment. During the initial 45 minutes post-infusion, participants were encouraged to relax with their eyes closed and maintain a supine position while listening to music by the ambient music artists "Stars of The Lid". This music was only played during the initial 45 minutes, and not during the subsequent psychological testing.

Participants reported first noticing subjective drug effects between 5 to 15 minutes post-dosing, and these approached peak intensity between 45 to 90 minutes post-dosing. The duration of a subsequent plateau of drug effects varied among individuals but was generally maintained for approximately three hours post-dosing. Psychological tests were performed within this time-frame. Five music tracks were played to each participant during each session at the following time points post-dosing (minutes: mean, SD): 44 ± 17 (Track 1), 101 ± 25 (Track 2), 139 ± 33 (Track 3 and 4) and 250 ± 53 (Track 5). The time in between the tracks, participants either spent relaxing or performing tasks that were part of separate experiments and therefore not reported here. Once the subjective effects of LSD had sufficiently subsided participants completed a 29-item questionnaire enquiring about the drug's subjective effects (Carhart-Harris et al., 2012, 2011). Following this, the study psychiatrist assessed the participant's suitability for discharge. Participants remained in the research centre for an average of six hours post-infusion.

3.2.5 Stimulus selection and task design

Two playlists were compiled (A and B), each containing five different music tracks. One version was heard on the first study day and the other on the second, with the order of the playlists counterbalanced across participants. The emotional potency of the two lists was balanced based on pre-study ratings from a separate sample (n=10). Pre-ratings were provided for 16 instrumental music tracks of the classical, neo-classical, ambient and new-age genres using the GEMS-9. In addition, the tracks were also rated for general liking and familiarity. It was from the subsequent ratings that 10 tracks were selected for the study. Specifically, tracks were chosen that produced highest liking and lowest familiarity, and a two-tailed paired t-test confirmed no significant differences between the playlists on liking, familiarity and GEMS-9 scores. The final five tracks selected for each playlist consisted of neo-classical and ambient music composed by the following four contemporary musicians: Greg Haines, Ólafur Arnalds, Arve Henriksen and Brian McBride (see table 3.1). Each music track and all rating scales were presented via Psychopy presentation software (Peirce, 2009).

Before listening to a music track, participants were instructed to close their eyes and relax. Music was played via high-quality stereo headphones (Beyerdynamic DT990 Pro) and participants were allowed to adjust the volume via remote volume control. When the music ended, a pre-recorded voice instructed them to open their eyes. They were then presented with the question "how emotionally affected were you by the music?" Participants gave ratings via a continuous visual analogue scale from 0 ("not at all") to 100 ("very much"). Following this, a digitalized and shortened version of the full GEMS, the GEMS-9, was presented (Zentner et al., 2008). A particularly important instruction given prior to completing the questionnaire was that participants should rate how he or she personally felt *in response to* the music, and not what he or she thought the music was trying to communicate to them or how he or she felt in general. The GEMS-9 consists of 9 items or categories of emotion, with sub-items presented in brackets: wonder (filled with wonder, dazzled, moved), transcendence (fascinated, overwhelmed, feelings of transcendence and spirituality), power (strong, triumphant, energetic), tenderness (tender, affectionate, in love), nostalgia (nostalgic, dreamy, melancholic), peacefulness (serene, calm, soothed), joyful activation (joyful, amused, bouncy), sadness (sad, sorrowful), tension (tense, agitated, nervous). Each item was scored from 0 to 4: 0 = "not at all", 1 = "somewhat", 2 = "moderately", 3 = "quite a lot", and 4 = "very much".

3.2.6 Data analysis

All statistical tests were performed in Statistical Package for the Social Sciences (SPSS) for Windows, Version 21.0. Scores for the question "how emotionally affected were you by the music?” for each stimulus were averaged for each subject per condition. A paired two-tailed t-test was performed to test for significant difference between conditions. Since the 5 possible ratings for the GEMS-9 were ascribed a relevant number (e.g. 0 = “not at all”, 1 = “somewhat”) and the resultant data was normally distributed, two-tailed paired t-tests were used to analyse between-condition differences. Subsequent false discovery rate (FDR) control was used to correct for multiple comparisons (Benjamini & Hochberg, 1995).

Finally, a Pearson’s correlational analysis was performed to evaluate a hypothesised relationship between the peak intensity of LSD’s subjective effects and the intensity of emotional arousal in response to music under LSD (i.e. the average score for all music stimuli to the question “how emotionally affected were you by the music?”) as well as the relationship between peak drug intensity and increases in the GEMS-9 item “transcendence”.

Table 3.1 | The two music playlists.

		Playlist A		Playlist B	
Stimulus	Artist name	Track title	Duration	Track title	Duration
1	Greg Haines	183 Times	09:08	Azure	14:14
2	Brian McBride	Toil theme part 2 & part 3	05:11	Supposed Essay on the Piano	04:10
3	Ólafur Arnalds	The Wait	03:35	Autumn Day	03:26
4	Brian McBride	Mélodrames Télégraphiés Part 2	04:12	Mélodrames Télégraphiés Part 1	05:25
5	Arve Henriksen	In the Light	05:29	Leaf and Rock	02:17

3.3 Results

3.3.1 Participants

Ten healthy volunteers participated in the study (1 female; mean age = 34.2 ± 7.4, range = 26-47 years). All had at least one previous experience with a classic psychedelic drug (mean estimated LSD uses = 65 ± 90, range = 0 - 250) but not within 21 days of the study (mean last use of LSD = 1829 ± 2348, range = 30-5000 days). Self-estimates of other drug use were as follows (mean, SD, range): weekly alcohol units = 9.2 ± 9.1, 0-26; daily cigarettes = 3.5 ± 6.6, 0-20; lifetime cannabis uses = 822 ± 377, 20-1000; lifetime MDMA uses = 79 ± 117, 3-400; lifetime psilocybin/magic mushroom uses = 19.5 ± 14, 6-40; lifetime ketamine uses = 51 ± 84, 0-200; lifetime cocaine uses = 23.1 ± 31, 0-100. Beck Depression Inventory scores at baseline were: 1.9 ± 1.6, 0-4; NEO-FFI scores were: neuroticism = 13.2 ± 6.5, 5-26; extraversion = 32 ± 8, 20-44; openness = 31 ± 3.8, 26-35; agreeableness = 35.7 ± 4.1, 32-45; conscientiousness = 34.2 ± 6.5, 25-42.

3.3.2 Physiological effects of LSD

Measurements of blood pressure and heart rate under placebo and LSD are displayed in table 3.2. Systolic blood pressure was slightly elevated under LSD relative to baseline and placebo but these changes were not statistically significant after correcting for multiple comparisons.

Table 3.2 | Physiological measurements for placebo and LSD. Values (millimeters of mercury (mmHg) for blood pressure, and beats per minute (bpm) for heart rate) are displayed in rounded mean values + standard error of the mean.

	Systolic blood pressure		Diastolic blood pressure		Heart rate	
	Placebo	LSD	Placebo	LSD	Placebo	LSD
Baseline	125± 5	123 ± 4	72 ± 4	78 ± 4	78 ± 5	77 ± 5
45th minute	120 ± 3	132 ± 6	69 ± 3	76 ± 4	75 ± 4	77 ± 4
180th minute	n.a.	n.a.	n.a.	n.a.	65 ± 3	79 ± 5
End	118 ± 3	134 ± 5	68 ± 3	74 ± 4	68 ± 3	74 ± 4

3.3.3 Subjective effects of LSD

Subjective drug effects were first noticed between 5 to 15 minutes post-LSD and approached peak intensity between 45 to 90 minutes post-dosing. Drug effects maintained a subsequent plateau for approximately three hours, and showed a gradual decline in the following hours. These results suggest that compared with oral administration of LSD (Schmid et al., 2015;

Passie et al., 2008; Nichols 2016), intravenous administration produces a quicker onset, and (slightly) shorter lasting experience. LSD produced diverse subjective effects (see Figure 3.1). The five VAS items that were scored highest under LSD were (in descending order) were "my thoughts wandered freely", "my imagination was extremely vivid", "I felt amazing", "things looked strange" and "I felt an inner warmth".

3.3.4 Effects of LSD on music-evoked emotion

The average scores for all music stimuli to the question "how emotionally affected were you by the music?" were significantly higher for the LSD condition (0.71 ± 0.14) than for placebo (0.51 ± 0.18), t = 3.559, df = 9, p = 0.006 (see Figure 3.2). Significant increases were observed in the GEMS for the items "wonder" (p=0.027), "transcendence" (p=0.027), "power" (p=0.027) and "tenderness" (p=0.027) (reported p-values are FDR adjusted, see Figure 3.3).

3.3.5 Effects of LSD on music liking

The average scores for "liking" the music showed a trend-level significant increase under LSD (0.80 ± 0.14) compared to placebo (0.71 ± 0.06), df = 9, p = 0.06. A Pearson correlation test revealed a significant positive correlation between "liking" of the music and VAS ratings on the question "how emotionally affected were you by the music?" (R = 0.68, p <0.001, n = 100) (see Figure 3.4). A significant positive relationship was found between ratings of the intensity of LSD's effects and emotional arousal to music (r = 0.79, n = 10, p = 0.01), as well as between the former and increases in the GEMS-9 factor "transcendence" (r = 0.79, n = 10, p = 0.01).

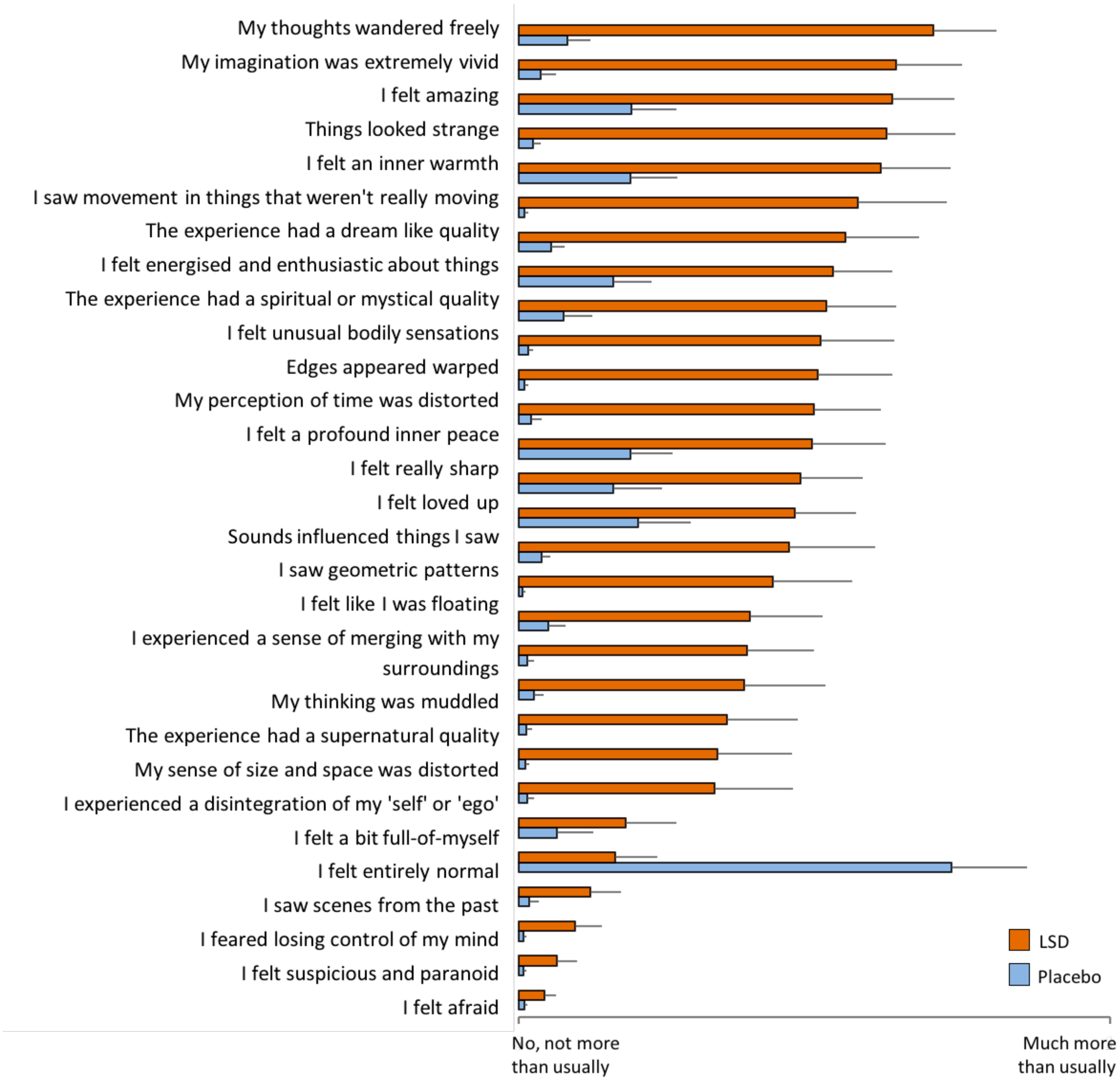

Figure 3.1 | Subjective effects of LSD. Group averages plus standard error values for all VAS scored subjective effect after placebo (blue) and after LSD (red). All ratings were given with reference to peak drug effects.

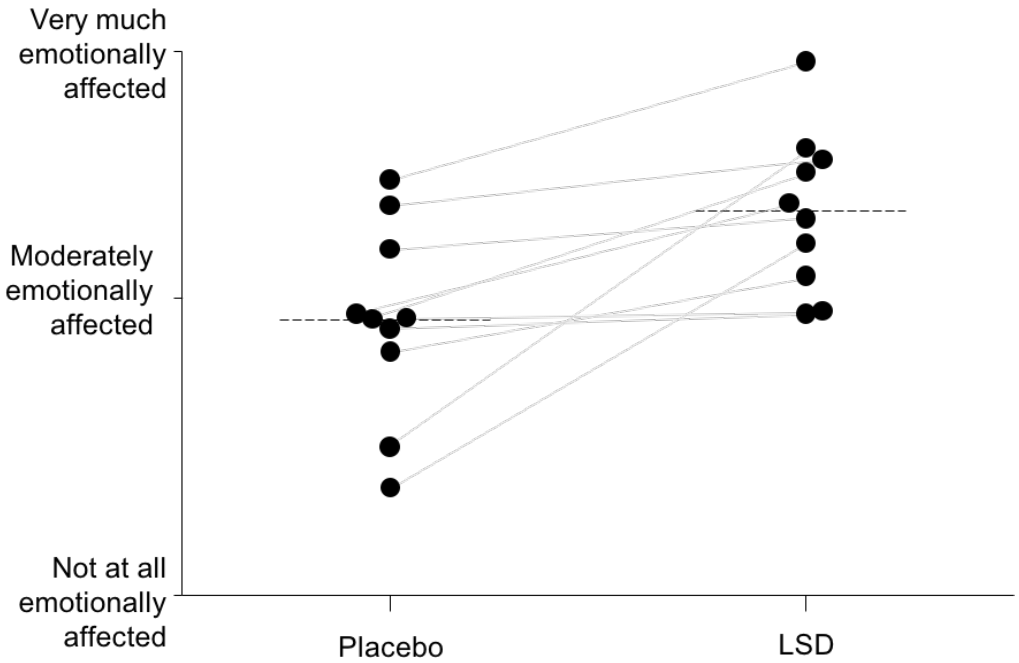

Figure 3.2 | Effect of LSD on music-evoked emotion. Each data point represents one participant's average response (average rating from the five songs) to the question "How emotionally affected were you by the music?" The dotted horizontal line represents the group average for each condition. The lines connecting the data points demonstrate the individual increases in emotional arousal to music from placebo to LSD. Participants gave significantly higher ratings under LSD than placebo, t = 3.559, df = 9, p = 0.006.

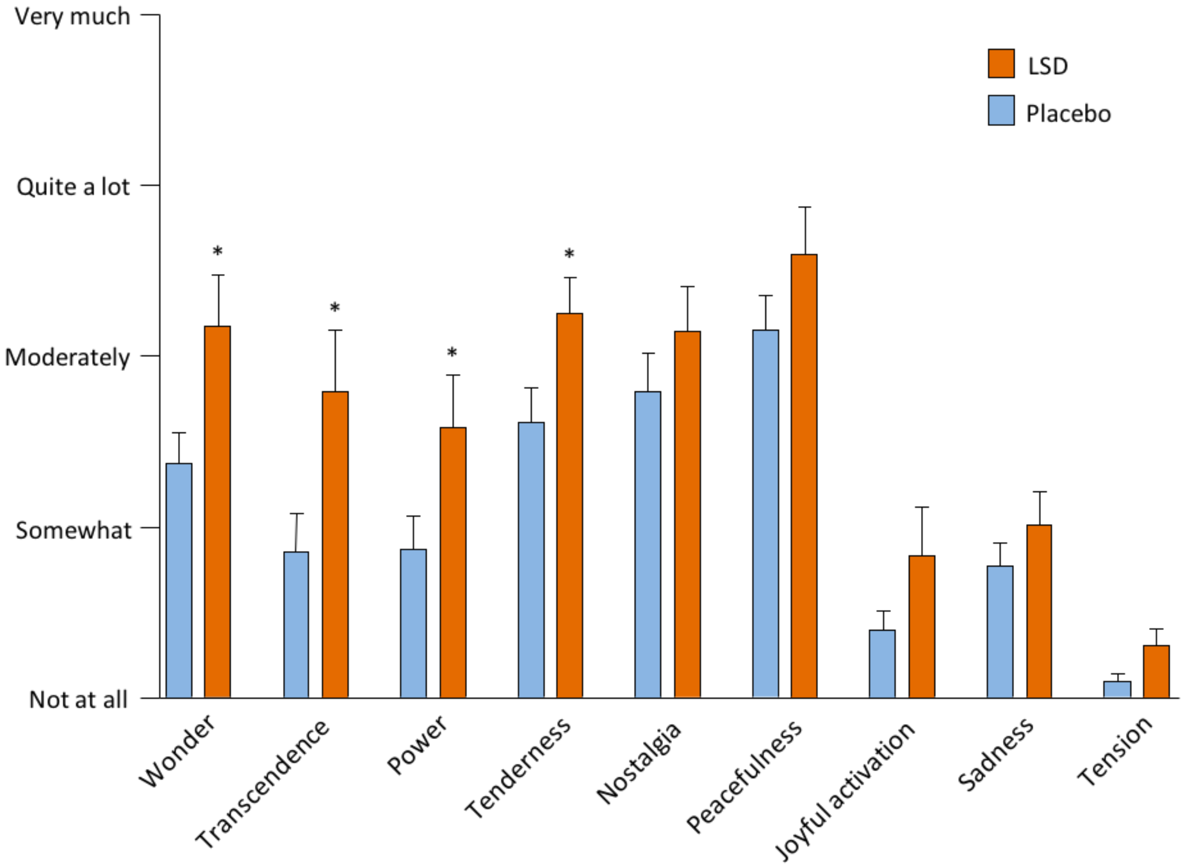

Figure 3.3 Geneva Emotional Music Scale (GEMS). Mean plus standard error values for the GEMS-9 scores for the complete playlist per condition. Scores were significantly higher for the LSD condition than placebo for the items "wonder" (p=0.027), "transcendence" (*p*=0.027), "power" (*p*=0.027) and "tenderness" (*p*=0.027). Reported P-values are FDR adjusted. * = $p < 0.05$ after FDR correction for multiple comparisons.

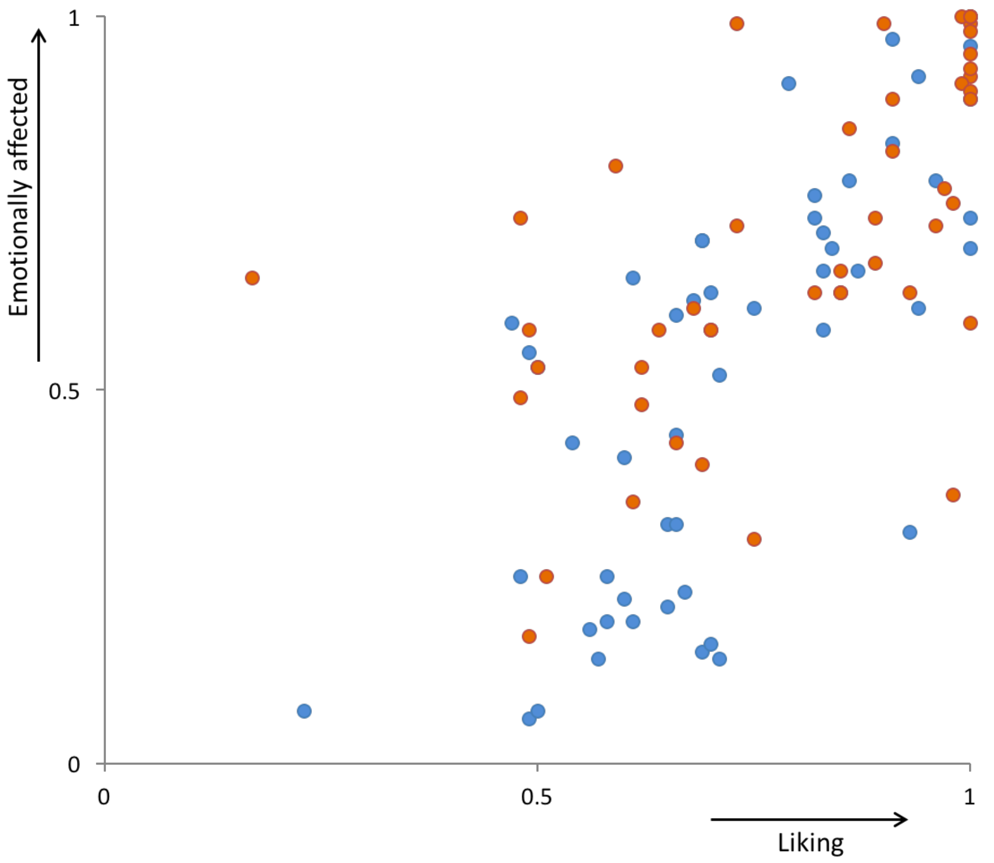

Figure 3.4 | Correlation between "liking" and the emotional response to music. Each data point represents one rating for one song per participant and per condition (Blue = placebo, red = LSD). A Pearson correlation test demonstrated a significant positive correlation between ratings for "liking" of the music and ratings for "how emotionally affected were you by the music?" ($R = 0.68$, $p<0.001$).

3.4 Discussion

This study assessed changes in music-evoked emotion under LSD. The primary hypothesis that music-evoked emotions are intensified under LSD was supported, as was the more specific hypothesis that music-evoked emotions related to peak experiences showed an increase under LSD. Ratings for the Geneva Emotional Music Scale (GEMS) were significantly higher under LSD for the emotions "wonder" (i.e. filled with wonder, dazzled, moved), "transcendence" (i.e. fascinated, overwhelmed, feelings of transcendence and spirituality), "tenderness" (i.e. tender, affectionate, in love) and "power" (i.e. strong, triumphant, energetic). Ratings for drug intensity correlated positively with ratings for emotional arousal to music, as well as with music-evoked feelings of "transcendence". In addition, the study also showed a trend increase for ratings of music-liking under LSD, and a positive correlation between music-liking and the emotional-response to music.

3.4.1 Implications for psychedelic therapy

These findings reinforce the assumption that normal musical influences are intensified under psychedelic drugs, and that this effect may be harnessed for therapeutic objectives. Typically, the conditions in which psychedelic therapy sessions are performed, are intended to promote a state of enhanced "introspection", where music constitutes the only external stimulus: Individuals lie supine in a relaxed position, close their eyes or wear eye-shades, and listen to a music for the duration of the drug-effects (5-8 hours). Under these conditions, peak experiences can be reliably facilitated (Pahnke and Richards, 1966; Griffiths et al., 2008; Griffiths et al., 2011), and the occurance of these experiences has been correlated with sustained improvements in well-being (Johnson et al., 2008; RolandGriffiths et al., 2011), increases openness (MacLean et al., 2011), and improved therapy outcomes (Griffiths et al., 2016; Ross et al., 2016; Garcia-Romeu et al., 2014).

Emotions of transcendence and wonder are considered core constituents of peak- and spiritual experiences (Maslow, 1971, 1964). Thus, the ability of music to evoke these emotions, and of LSD to facilitate an enhancement of these music-evoked emotions, suggests that their combination may contribute to the occurrence of peak experiences. If peak experiences are associated with the sustained therapeutic effects of psychedelic therapy, and if the likelihood of their occurrence can be increased by music, then this would support the view that music is a valuable component within psychedelic therapy.

3.4.2 Study limitations and future directions

This experiment had several important limitations that need to be addressed. First, LSD has been found to enhance suggestibility (Carhart-Harris et al., 2014), and such an effect may have influenced the present findings. Participants were not informed of our hypotheses, but it would not have been difficult for them to have inferred them from the experimental procedures. Participants' ratings for the question "how emotionally affected were you by the music", may have been higher to reinforce their own expectations or to confirm (their perception of) the researchers'. In addition, the discernible subjective effects of LSD make it difficult, if not impossible, to maintain study blind, and may have compounded any of such biases.

Therefore, measures to reduce expectation or increase uncertainty about the experimental aims could be introduced in future studies. For example, variable doses of LSD and a larger sample size would allow to examine dose-dependent effects of the present findings. In addition, physiological measures for emotional arousal could also be introduced, such as the measure of "chills" via changes in galvanic skin response, which have previously been related to emotional arousal to music (Juslin and Sloboda, 2010). Secondly, an active control would strengthen the blinding of the conditions in individuals who are naïve to subjective effects of psychedelics. For example, Griffith et al (2008) utilised methyl-phenidate as an active placebo condition, and found some participants to be "fooled" by the condition (Griffiths et al., 2008). In addition, alternative pharmacological conditions could serve to probe into mechanistic hypotheses. For example, if the effects of psychedelics are instantiated via serotonin 2A receptor activation, co-administration with a selective serotonin 2A receptor antagonist would be predicted to significantly diminish the effects of the psychedelic on music-evoked emotion. This hypothesis is supported by a body of animal research suggesting an important role for serotonin 2A receptor activation in emotion regulation and emotion-guided behaviour (Aznar and Klein, 2013).

Another limitation of the experiment is that it did not have a balanced order, i.e. all participants received placebo on the first visit, and LSD on the second visit. Randomising or at least balancing the order of the LSD and placebo sessions be worth incorporating into the design of future studies to control for potential effects of order. However, it is unlikely that order contributed significantly to the present outcomes, given that the music playlists were balanced across participants and days, and order effects are typically sensitive to elements like learning and habituation. However, it may be argued that by the second visit in this experiment, participants may have been more familiar with the study procedure and study environment, and that this could have positively influenced their ability to be emotionally affected, thereby introducing a bias towards a positive finding.

One other major limitation of this experiment concerns its ability (or lack thereof) to differentiate between the effect of drug and the effect of music. The experiment did not assess emotion pre- and post-music, but assessed the magnitude of being emotional affected by the music after listening. Without pre- and post- music ratings implemented within a factorial design, this experiment cannot exclude the possibility that the findings are driven by a general drug effect rather than a specific effect of music in combination with drug. The positive correlation between drug effects intensity and increased feelings of "transcendence" to music could be construed as supportive of this alternative interpretation. Alternatively, however, stronger drug effects may have simply enhanced a true music x LSD interaction.

In defence of the present findings, both the ratings for "How emotionally affected were you by the music?", as the ratings for GEMS-9, explicitly requested that the participant rate how the music made them feel and not how they felt in general or what they thought the music was intending to convey. While no formal statistical tests for an interaction between drug and music on emotion was performed, the questions were intentionally constructed to enquire about *the effect of music on emotion*. This does allow to interpret the findings as differences in *music-evoked* emotion between the two conditions. Nevertheless, to investigate an interaction between drug and music on emotion, a factorial design will need to be performed, since the absence of such a design in the present study prevents a formal rejecting of the hypothesis that the results were driven by a general drug effect.

Other limitations of the study design that future studies can address include studying the route of drug-administration, and identifying advantages of IV over oral administration. The assumption that a fixed-order design (with drug on the first), prevents possible “residual” psychological effects on the second study day, must be tested. Also, it is important to emphasise that this was a pilot study with a small sample size. Future studies with larger sample sizes, could address the dose-response relationship of LSD by including sufficient numbers of participant within different dose-groups. Moreover, only one female was recruited, all participants were psychedelic-experienced and only a selection of music styles were included. Inferences on the present results can therefore not be generalised beyond the music styles used in the present study and neither can they be easily generalised to larger populations. Future studies could assess the importance of specific genres or styles of music and the effect of individual music taste in determining outcomes in response to psychedelics.

3.4.3 Conclusions

The results of this experiment provide tentative support for the hypothesis that psychedelics enhance music-evoked emotion, yet more extensive studies are required to confirm and extend the inferences that have been discussed here. Specifically, more studies are warranted to probe into the relation between drug-effect and music-effect on subjective experience, as well as studies that test the importance of music as a component in psychedelic therapy, and studies that investigate *how* psychedelics enhance the emotional response to music via their effect on brain activity. These will be the objectives of the subsequent experiments.

"My flesh is charged with emotional responsiveness to the Mozart E-flat symphony. My skin seems microscopically thick and porous as to admit the music more easily. The inner lines of counterpoints are suddenly so clear. The dissonances are so penetrating and the bass-line is positively alive. It jumps and strides with a kind of cosmic purpose. […] I felt that I saw directly into its heart, and was interested only in what the music was really saying."

LSD-experience by anonymous

4 *Study 2* | Effects of LSD and music on brain activity and emotion

4.1 Background

The quote that opens this chapter is provides a glimpse into how profound the subjective experience of music can be under a psychedelic. Similar reports are not difficult to find, and the widespread historical use of psychedelics and music by humans (Nettl, 1956; Bruhn et al., 2002), may very well be related to their capacity to evoke such deeply idiosyncratic experiences. The potential of music on its own to evoke "complex" emotions, such as feelings of wonder and self-transcendence, as opposed to merely "simple" or "basic" emotions such as fear and pleasure, has been argued to yield an important tool for studying the neural correlates of human emotions (Trost et al., 2012). Music allows a relatively reliable activation of complex emotions under experimental conditions, such as feelings of nostalgia (Barrett and Janata, 2016; Janata 2009) or intense emotional experiences (Gabrielsson and Wik, 2003). Psychedelic drugs are shown to reliably facilitate emotionally intense peak experiences under music-listening conditions (Griffiths et al., 2006; Griffiths et al., 2011), and the findings reported in the previous chapter (study 1) indicated that music may play an important function in facilitating these experiences. Studying the brain mechanisms of music-listening under psychedelics will help to understand how they interact on subjective experience, what their therapeutic potential may be when used in combination, and to provide empirical insights on how music may be best implemented in psychedelic therapy sessions.

Studying music brings unique experimental challenges and opportunities, because music is a highly dynamic and multi-dimensional stimulus. Music consists of distinct acoustic features, such as pitch, loudness, tempo, rhythm and timbre, and neuroimaging studies with music have highlighted a hierarchy of processes (Stewart et al., 2008; Kumar et al., 2007); ascending from the cochlear, the auditory system processes increasingly complex acoustic features that are subsequently integrated via multi-modal and higher-order cortical regions that furnish the experience with mnemonic and affective properties (Wang et al., 2008; Bizley and Cohen, 2013; Griffiths and Warren, 2004). Several neuroimaging studies have used controlled auditory experiments to study acoustic features in isolation, however, recent studies advocate the use of more naturalistic paradigms in which participants listen to real, extended pieces of music. These naturalistic conditions, increase the ecological validity and obtain a more comprehensive description of the brain mechanisms involved in processing the complexity inherent in real musical stimuli and the complex emotionality they can evoke (Alluri et al., 2012; Burunat et al., 2016), such as those emotions that are associated with peak experiences.

Psychedelics activate the serotonin 2A receptor (Glennon et al., 1984; Titeler et al., 1988a; Vollenweider et al., 1998), and produce an altered state of consciousness that is characterised by marked reductions in functional coupling within high-level brain networks (Carhart-Harris et al., 2016, 2012; Palhano-Fontes et al., 2015), and simultaneous increased cross-talk between low-level areas (Tagliazucchi et al., 2016, 2014). This “collapse” of the usual processing hierarchy, is thought to be a core mechanism underlying their subjective effects (Carhart-Harris et al., 2014; Lebedev et al., 2015). This study intends to investigate the changes in brain processing of distinct acoustic features in under naturalistic music-listening conditions under LSD. The primary aim of this study was to identify what specific features of music are most sensitive to modulation by LSD, and how this relates to the changes in music-evoked emotions under LSD. More broadly, this experiment can offer insight into the brain’s processing of complex naturalistic stimuli accompanying this network collapse under psychedelics.

4.2 Methods

4.2.2 Participants

Twenty participants (16 males and 4 females) were recruited for the study after successful screening and written informed consent. Screening consisted of physical and mental health assessments. Physical health assessments included electrocardiogram (ECG), routine blood tests, disclosure of full medical history and urine test for recent drug use and pregnancy. Mental health assessment consisted of psychiatrics interview. All participants provided full disclosure of their drug use history. Exclusion criteria included: being younger than 21 years of age, having a personal history of diagnosed psychiatric illness, having an immediate family history of a psychotic disorder, having used illicit drugs within 6 weeks of the first scanning day, having experienced a persistent adverse reaction to a psychedelic drug, pregnancy, problematic alcohol-use (i.e. > 40 units consumed per week), and having a medical condition rendering them unsuitable for the study. All participants were required to have at least one previous experience with a classic psychedelic drug (E.g. LSD, mescaline, psilocybin or dimethyltryptamine (DMT)). One participant did not complete the MRI scans due anxiety and three participants were excluded from analyses due to technical problems with the sound delivery. This resulted in including the data of 16 participants (13 males, 3 female) in the data-analysis; with preserved counterbalanced experimental design.

4.2.3 Stimuli

Two excerpts (A and B) from two songs by musician's Robert Rich & Lisa Moskow were selected for the study (form the album *yearning*). The stimuli were both 7 minutes and 20 seconds long and were balanced in their acoustic properties, and rich in timbre, but not in rhythm (see table 4.1). Pre-study assessments using GEMS in a separate group confirmed balance for their emotional potency (n=10). To reduce interference of fMRI scanning noise with the music experience, volume-maximization and broadband compression was carried out using Ableton live 9 software. Each participant listened to both stimuli, in a balanced order across conditions. The selective choice for calm ambient music for this study, was motivated by a study from Studerus et al (2012), who performed a regression analysis on pooled data from 261 healthy volunteers, showing that under the influence of psilocybin, neuroimaging, together with trait “emotional excitability”, are strong predictors for anxiety. That ambient music can compensate for this, however, is an assumption. Trade-offs of genre-selection for this study, and implications for future studies, will be provided in more detail in the discussion section.

4.2.4 Experiment overview and procedures

All participants attended two study days that were separated by at least 14 days. LSD was received on one of the study days, and placebo (saline) on the other. The condition-order was balanced across participants, and the participants, but not the researchers, were blind to the condition-order (i.e. the study was a single-blind within-subject design). All participants received 75 µg of LSD intravenously, via a 10ml solution infused over a two-minute period via an inserted cannula. Administration was always followed by an acclimatization period of approximately 60 min, in which participants were encouraged to relax. Drug effects were noticed between 5 to 15 min post-dosing, approached peak intensity between 60 to 90 min post-dosing, and maintained peak intensity for approximately four hours post-dosing. BOLD fMRI scanning was performed during peak drug intensity, starting approximately 120 minutes post-dosing, and lasted for approximately 60 minutes. Once the subjective effects of LSD had sufficiently subsided, the study psychiatrist assessed the participant’s suitability for discharge.

Each fMRI scanning session involved three eyes-closed resting state scans, each lasting seven minutes and twenty seconds. The music-listening scan (220 TRs, 7.3 min) always occurred after the first resting state (no music) scan and before a final resting-state scan (no music). Prior to each scan, participants were instructed via a display screen to close their eyes and relax. The music itself was triggered by the first TR, and listened to via MR compatible headphones (MR Confon). Music volume was adjusted to a personal level that was “loud, but not unpleasant” and maintained for both condition.

Table 4.1 | Average values for all acoustic features. Displayed values are the calculated average and standard deviation for acoustic features extracted from stimulus A and B.

	STIMULUS A		STIMULUS B	
ACOUSTIC FEATURE	Mean	SDev	Mean	SDev
LOUDNESS	0.17	0.04	0.20	0.04
BRIGHTNESS	0.13	0.03	0.14	0.04
ROUGHNESS	51.41	25.42	92.27	36.44
FLATNESS	0.04	0.01	0.04	0.00
SPECTRAL ROLL-OFF	1317.61	250.70	1437.68	243.82
CPEXTRAL CENTROID	907.33	99.68	966.11	117.57
SPREAD	1932.38	114.73	1901.17	95.45
ENTROPY	0.61	0.03	0.62	0.03
SPECTRAL FLUX	54.75	11.42	50.51	10.31
ZERO-CROSS	416.79	99.44	490.04	138.06
SPECTRAL FLUX SUBBAND 1	11.71	5.21	4.21	3.93
SPECTRAL FLUX SUBBAND 2	15.00	6.02	11.16	4.66
SPECTRAL FLUX SUBBAND 3	9.71	4.40	13.78	4.24
SPECTRAL FLUX SUBBAND 4	5.86	2.52	8.47	3.22
SPECTRAL FLUX SUBBAND 5	2.97	0.98	5.86	2.74
SPECTRAL FLUX SUBBAND 6	1.50	0.55	1.91	0.82
SPECTRAL FLUX SUBBAND 7	0.62	0.26	1.22	0.67
SPECTRAL FLUX SUBBAND 8	0.15	0.08	0.26	0.14
SPECTRAL FLUX SUBBAND 9	0.13	0.08	0.13	0.07
SPECTRAL FLUX SUBBAND 10	0.06	0.03	0.06	0.03
PULSE CLARITY	0.23	0.09	0.22	0.08
KEY CLARITY	0.69	0.10	0.74	0.07
MODE STRENGTH	0.01	0.11	-0.06	0.09

4.2.5 Qualitative measurements

The intensity of different types of music-evoked emotion was assessed via the 25-item Geneva emotional music scale (GEMS) (Zentner et al., 2008), and was administered under placebo and under LSD immediately after fMRI scanning was completed. The GEMS assesses music-evoked or "personally felt" emotion, and not the perception of musical emotion in the music. The 25 items were averaged into nine distinct factors of emotions: wonder, transcendence, power, tenderness, nostalgia, peacefulness, joyful activation, sadness, and tension. A paired t-test was performed to compare ratings between conditions (LSD versus placebo) for each emotion. Non-parametric permutation testing (10,000 permutations, two-tailed) was carried out to correct for multiple comparisons.

4.2.6 Acoustic feature extraction

Acoustic features from excerpt A and B were extracted separately using the Music Information Retrieval (MIR) toolbox (version 1.6.1) (Lartillot and Toiviainen, 2007), implemented in MATLAB. Selection of acoustic features was informed by Alluri et al (2012, 2013), who identified 25 features that broadly capture the dynamics of the timbral, tonal and rhythmic properties present in the music stimuli. From the original 25 features we excluded fluctuation entropy and fluctuation centroid because they have not been studied in the literature and did not carry any valid perceptual meaning (Alluri et al., 2012, Alluri 2016 personal communication). The 23 acoustic features used in our analyses were categorized in short-term features and long-term features (for an overview see Table 4.2). The short-term features were extracted with a sliding window of 25 ms, with 50% overlap between each segment while for the computation of the long-term features a longer sliding window of 3 s was employed, with 33% overlap between each segment (following the approach in Alluri et al., 2012, 2013). Subsequently, principle component analysis (PCA) on the acoustic features (combined for excerpt A and B) was performed to (1) identify acoustic properties that are present in both excerpts and (2) to reduce the number of regressors that entered the general linear model (GLM) for fMRI analyses. To prepare the acoustic features for the PCA, we first resampled short and long-term features to the same sampling rate of 1 s. We then rescaled (between 0 and 1) those acoustic features separately that were computed by different MIR toolbox functions (i.e., measured on different scales) whilst rescaling acoustic features combined that were computed by the same MIR toolbox function (i.e., measured on the same scale as the case for the 10 sub-band flux features) in order to preserve their covariance structure. The resulting time courses for excerpt A and B were then concatenated, to undergo the PCA. We performed varimax rotation on the first eight principal components

(PCs) that explained over 90% of the variance (see Figure 4.2 for rotated PCs and their respective loadings).

In order to validate that the first eight PCs explained the two excerpts equally well (i.e., that PCs were not driven by either one excerpt or the other), we correlated (Pearson r) each of the 23 predicted timeseries (by multiplying the eight rotated PC loadings with the 23 PC time courses) with the corresponding acoustic features for the two excerpts separately. Across all 23 acoustic features, we found a mean ± SD r of 0.9098 ± 0.0919 for excerpt A and 0.8835 ± 0.1037 for excerpt B (for correlation values per acoustic feature, see Figure 4.1). As the difference in variance explained between the two excerpts was negligible, we used the time courses of the first eight rotated components for our subsequent analyses.

Next, we split the time courses of the rotated PCs to obtain timeseries corresponding to excerpt A and B, respectively. Those were then convolved with a double-gamma hemodynamic response function (HRF) to account for the hemodynamic delay, down-sampled to 2 s, to match the sampling rate of the fMRI data and high-pass filtered at the cut-off frequency of 0.01 Hz (same as fMRI data). The first 10 seconds (5 TRs) of each excerpt's timeseries were excluded for subsequent analysis in order to avoid any artefacts caused by the convolution operation. Those timeseries were then entered as regressors of interest into subject-level GLMs of the fMRI analysis.

Table 4.2 | Acoustic features used in the analysis. Derived from the Music Information Retrieval toolbox.

Short-term features
Zero crossing rate, spectral centroid, high energy–low energy ratio, spectral spread, spectral roll-off, spectral entropy, spectral flatness (Wiener entropy), roughness, RMS energy, spectral flux, and Sub-Band Flux (10 coefficients).
Long-term features
Pulse clarity, fluctuation centroid, fluctuation entropy, mode and key clarity.

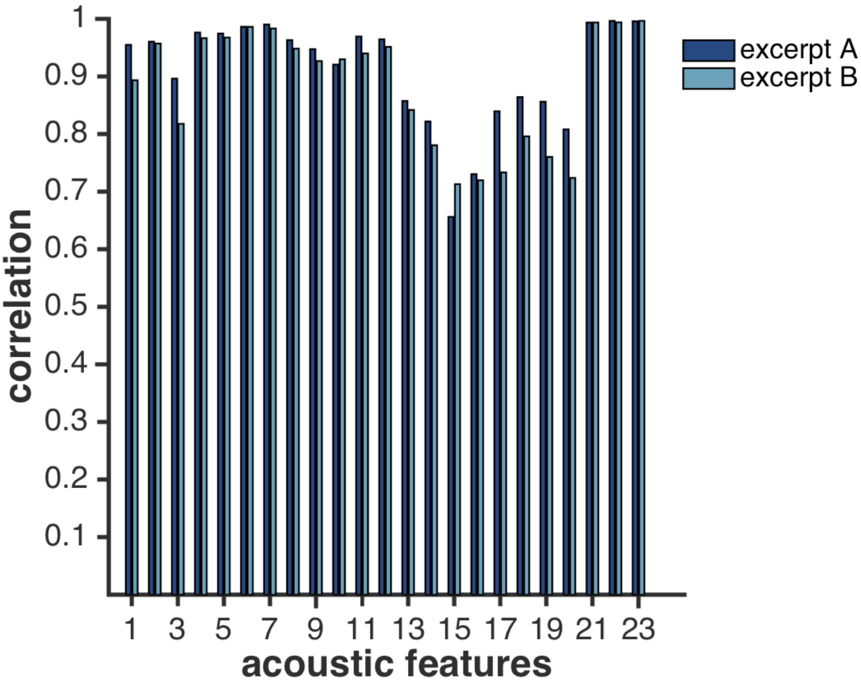

Figure 4.1 | Correlations of acoustic features. Significant correlations between the predicted timeseries and corresponding acoustic feature for both excerpts, indicate that the first eight PCs explained the two excerpts equally well.

4.2.7 fMRI scanning and data pre-processing

Neuroimaging was performed on a 3T GE HDx system. An initial 3D FSPGR anatomical scan was obtained in an axial orientation, with field of view = 256× 256× 192 and matrix = 256 × 256× 192 to yield 1-mm isotropic voxel resolution (TR/TE = 7.9/3.0 ms; inversion time = 450 ms; flip angle = 20°). This was used for registration and segmentation of functional images. Functional images were acquired using a gradient echo planer imaging sequence, TR/TE = 2000/35ms, field-of-view = 220mm, 64 × 64 acquisition matrix, parallel acceleration factor = 2, 90° flip angle. 35 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 BOLD scans was 7 minutes and 20 seconds.

The fMRI pre-processing pipeline was assembled from four complementary imaging software packages . 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. The following pre-processing stages were performed: 1) de-spiking (3dDespike, AFNI); 2) motion correction (3dvolreg, AFNI) by registering each volume to the volume most similar, in the least squares sense, to all others (in-house code); 3) brain extraction (BET, FSL); 4) rigid body registration to anatomical scans (eleven subjects with FSL's BBR, one subject with Freesurfer's bbregister and four subjects manually. Different software was required due variance in degrees in head-movement between participants); 5) non-linear registration to 2mm MNI brain (Symmetric Normalization (SyN), ANTS); 6) scrubbing (Power et al., 2012) - using a framewise displacement (FD) threshold of 1.0 mm; 7) spatial smoothing (FWHM) of 5mm (3dBlurInMask, AFNI) and high-pass filtering at a cut-off frequency of 0.01 Hz to remove baseline signal drifts. In addition, nine nuisance regressors were obtained: six were motion-related (3 translations, 3 rotations) and three 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) white matter (WM) (FSL's WM minus Freesurfer's subcortical grey matter (GM) structures, eroded in 2mm space). In order to cut the fMRI data and nuisance regressors to the same length as the PC time courses, we removed the first 5 TRs.

4.2.8 fMRI data analysis

We applied standard FSL FEAT GLM to determine the effect of PC time courses on BOLD activation. All eight PC time courses were entered as regressors of interest into subject-level GLMs in addition to their temporal derivatives and all nine nuisance regressors (resulting in 27 regressors in total). We then analysed the fMRI data with respect to eight contrasts (one contrast for each PC). The resulting individual subject-level contrasts were then entered into a high-level (mixed-effects) cluster-corrected FEAT analysis (FLAME 1+2) to obtain the paired t-test contrasts of LSD > Placebo and Placebo < LSD. In order to model out any potential effect of the order in which subjects listened to the different music excerpts under the different conditions, respectively, we included an interaction term in the higher-level FEAT as a regressor of no interest. We repeated the high-level analysis without the interaction term and obtained nearly identical results (not reported). All final group-level images were thresholded using a cluster correction threshold of Z > 2.3 and a cluster significance threshold of p = 0.05. Group-level images were visualized on an average surface brain using MRIcron (Rorden et al., 2007).

4.2.9 ROI selection and extraction for correlation analyses

Regions of interest (ROI) analysis was constrained to the group-level contrast LSD>Placebo for *timbral complexity* (i.e., PC3, see Results). ROI selection was based on previous literature and encompassed structures that have been commonly identified for music-evoked emotion (striatum, precuneus and insula) (Trost et al., 2012; Koelsch 2014), auditory perception (planum temporale and right IFG) (Griffiths and Warren, 2002b; Alluri et al., 2013, 2012; Zatorre and Salimpoor, 2013) and the subjective effects of psychedelics (precuneus and insula) (Muthukumaraswamy et al., 2013; Tagliazucchi et al., 2016; Carhart-Harris et al., 2016). ROIs were created by first selecting corresponding binarized structural areas from the Harvard-Oxford atlas (using a probability threshold of 10%) and then multiplying these with the group-level results to guarantee anatomical and functional specificity of the ROIs. Note that only the largest consecutive cluster of voxels were considered within each ROI. This procedure led to nine ROIs: right planum temporale, left planum temporale, right precuneus, right putamen, left putamen, right caudate, left caudate, right inferior frontal gyrus and right anterior insula (see table 4.3). The mean parameter estimates within each ROI were extracted for each participant, and Spearman’s rank correlation tests were used to relate the changes in parameter estimates (LSD > Placebo) with changes in GEMS-ratings for music-evoked emotions for the factors *wonder* and *transcendence* (LSD > Placebo). Non-parametric permutation testing (10,000 permutations, one-tailed) was carried out to correct for multiple comparisons (9 ROIs x 2 GEMS scales).

4.2.10 Psychophysiological interaction analysis

In order to assess *timbral*-specific changes in functional connectivity for the brain regions that showed a significant relationship with music-evoked feelings of wonder (i.e., precuneus and right inferior frontal gyrus, see Results), we conducted two separate psychophysiological interaction (PPI) analyses. For this, we first extracted subject-specific time courses from those ROIs and then applied standard FSL FEAT GLM. In addition to regressors that were included in the initial fMRI analysis (eight PC time courses, their temporal derivatives and nine nuisance regressors), we included the ROI timecourse (physiological regressor) and the PPI regressor that consisted of the element-wise multiplication of the physiological regressor with the timecourse encoding timbral complexity (psychological regressor, i.e. PC 3). The resulting individual subject-level contrasts were then entered into the same higher-level (mixed-effect) cluster-corrected FEAT analysis as described above (with an interaction term to model out the effect of “group”).

4.3 Results

4.3.1 Acoustic feature extraction

For acoustic feature selection and extraction, an approach similar to that described in Alluri et al. (2012, 2013) was used (Alluri et al., 2012, 2013). From the two musical excerpts used in the present study we extracted 23 acoustic features capturing tonal, rhythmical, and timbral properties that subsequently underwent a principle component analysis (PCA) to reduce the dimensionality of the data. The first eight principal components that together explained more than 90% of the variance were selected, and qualitatively were similar with the components identified in previous, independent studies (Alluri et al., 2013, 2012). The consistency of the identified components across musical genres (tango (Alluri et al., 2012), classic and pop (Alluri et al., 2013), as well as ambient music here) supports their reliability for representing fundamental acoustic properties in music. Importantly, perceptual validation and labelling for similar components has been demonstrated (Alluri et al., 2012). In the present study, a similar/comparable labelling for the principle components was therefore adopted (PCs) (Figure 4.1). In fact, when quantitatively comparing our PC’s with the PC’s from Alluri et al. (2012), medium to very high correlations (Pearson r) were found for fullness (r = 0.37, p = 0.08, df = 22), brightness (r =.96, p<0.001, df = 22), timbral complexity (r = .91, p<0.001, df = 22), key clarity (r = .96, p<0.001, df = 22) and pulse clarity (r = .96, p<0.001, df = 22).

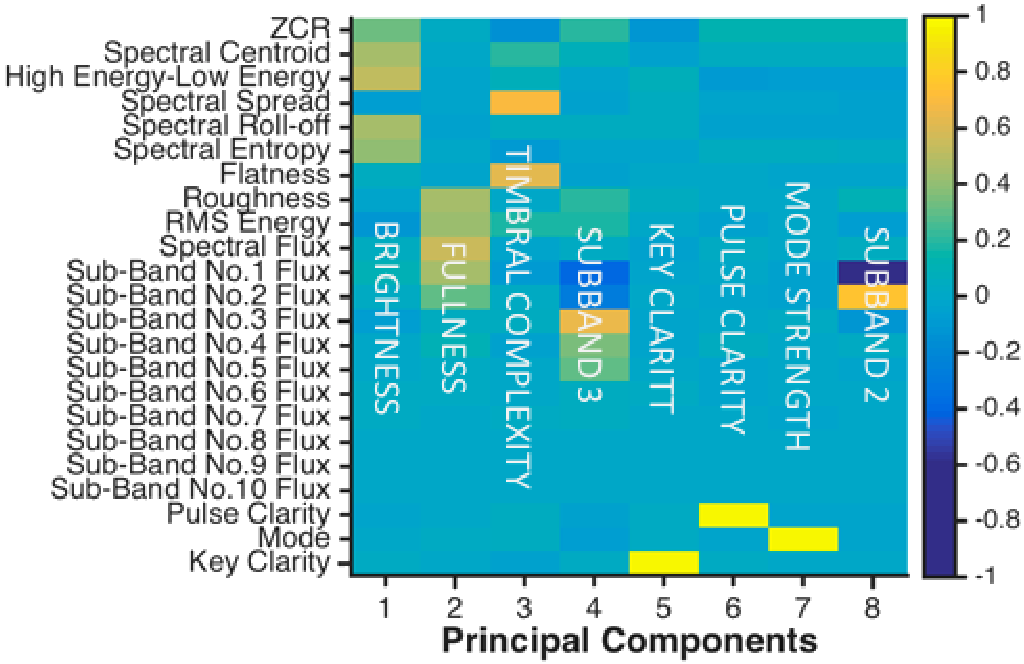

Figure 4.2 | Principle Component Analysis (PCA) of acoustic features. Loadings of the acoustic features on the first 8 PCs obtained from PCA followed by varimax rotation explained more than 90% of the variance. The x-axis shows the ordering of principal components, with the components ordered by explained variance. The colour bar corresponds to the strength of the loading for each acoustic feature for that components: warm colours indicates a positive loading, and cold colours a negative loading.

4.3.2 Effects of LSD on music-evoked brain activity

The time courses of the first eight PCs were entered into subject-level fMRI analyses as regressors of interests. Resulting individual subject-level contrasts were then entered into high-level analyses to obtain paired t-test contrasts of LSD > Placebo and Placebo < LSD. These analyses revealed altered blood-oxygen-level dependent (BOLD) responses under LSD for different acoustic components and within distinct cortical and sub-cortical areas. For the component *brightness*, decreases under LSD were observed in the left lateral occipital cortex (Figure 4.3A). For *fullness,* LSD increased activation in the bilateral thalamus, and decreased activation in the occipital cortex and right middle and inferior frontal gyrus (IFG) (Figure 4.3B). For *timbral complexity* increases under LSD were found in widespread cortical and subcortical networks, including auditory and auditory association cortices such as Heschl's

Gyrus, superior temporal gyrus (STG), and planum temporale as well as higher-level heteromodal cortices such as the precuneus, the right insula and the right IFG, bilateral striatum, the occipital cortex and the supplementary motor cortex. Increased BOLD activations to *timbral complexity* were more evident for left auditory cortices and more extensive in the right IFG and right anterior insula (Figure 4.3C). For the component *Subband 3* LSD significantly increased activation in occipital cortices while decreased activation in the cerebellum (Figure 3D). For *key clarity*, significant increases under LSD were observed in the right lateral occipital cortex, and decreases were found in the left striatum (Figure 4.3E). For the component *Subband 2,* LSD-related increases could be shown in the right lateral occipital cortex (Figure 4.3F).

BOLD changes under LSD appeared particularly pronounced to timbral complexity, and within brain networks commonly identified for music perception and emotion (Koelsch 2014; Alluri et al., 2012). ROI selection for connectivity analyses described below (paragraph 4.3.4) where therefore constrained to this contrast (see table 4.3 for ROI's). For insight into the effects of LSD and on timbral-complexity induced BOLD changes, parameter estimates from these ROI's for timbral complexity were plotted for placebo and LSD separately (see figure 4.4)

4.3.3 Effects of LSD on music-evoked emotion

Alongside investigating changes in music-evoked brain activity under LSD, our study aimed to assess the effects of LSD on music-evoked emotions. We measured nine different music-evoked emotions using the Geneva Emotional Music Scale (GEMS) that was completed by each participant after listening to music in each condition (Zentner et al., 2008). Paired t-tests on the GEMS scales revealed that, compared to placebo, music-evoked emotions were significantly higher under LSD for *wonder* ($t_{(18)}$=4.47, p=.002), *transcendence* ($t_{(18)}$=4.17, p=.004), *power* ($t(_{18})$=3.82, p=.008), *tenderness* ($t_{(18)}$=3.78, p=.008), *nostalgia* ($t_{(18)}$=3.94, p=.006), *peacefulness* ($t_{(18)}$=4.45, p=.003), and *joyful activation* ($t_{(18)}$=4.86, p=.001), but not for *sadness* ($t_{(18)}$=1.93, p=.25) or *tension* ($t_{(18)}$=1.42, p=.63) (Figure 4.5). P-values reported here are corrected for multiple comparisons using two-sided permutation testing with α set to .05. These results replicate the findings from study 1, demonstrating intensified music-evoked emotion under LSD.

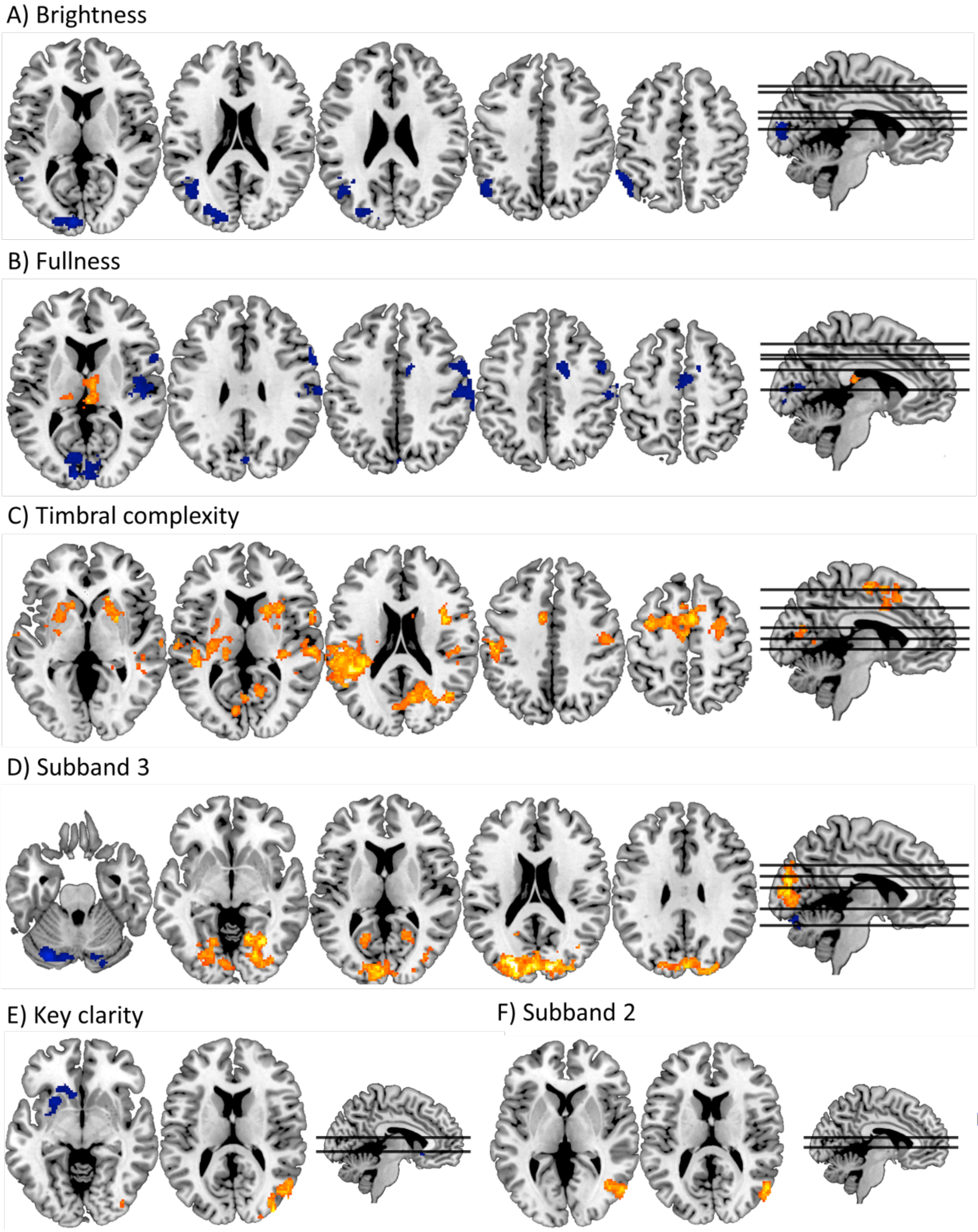

Figure 4.3 | Brain regions showing altered BOLD response to acoustic features under LSD. Increases (LSD>placebo) are displayed in yellow, and decreases (placebo>LSD) are displayed in blue. Cluster-correction was applied to all images with a threshold of Z > 2.3. Significant effects were observed in: **A)** *brightness*, with decreases in the occipital cortex, in **B)** *fullness*, with decreases in occipital cortex and right inferior frontal gyrus (IFG) and increases in bilateral thalamus, in **C)** *timbral complexity*, with increases in bilateral striatum, occipital cortex, supplementary motor cortex, auditory cortices, right insula and right IFG, in **D)** *subband 3*, with decreases in the cerebellum, and increases in the occipital cortice, in **E)** *key clarity*, with decreases in the left striatum and the right lateral occipital cortex, and finally, in **F)** *subband 2*, with increases in the right occipital cortex.

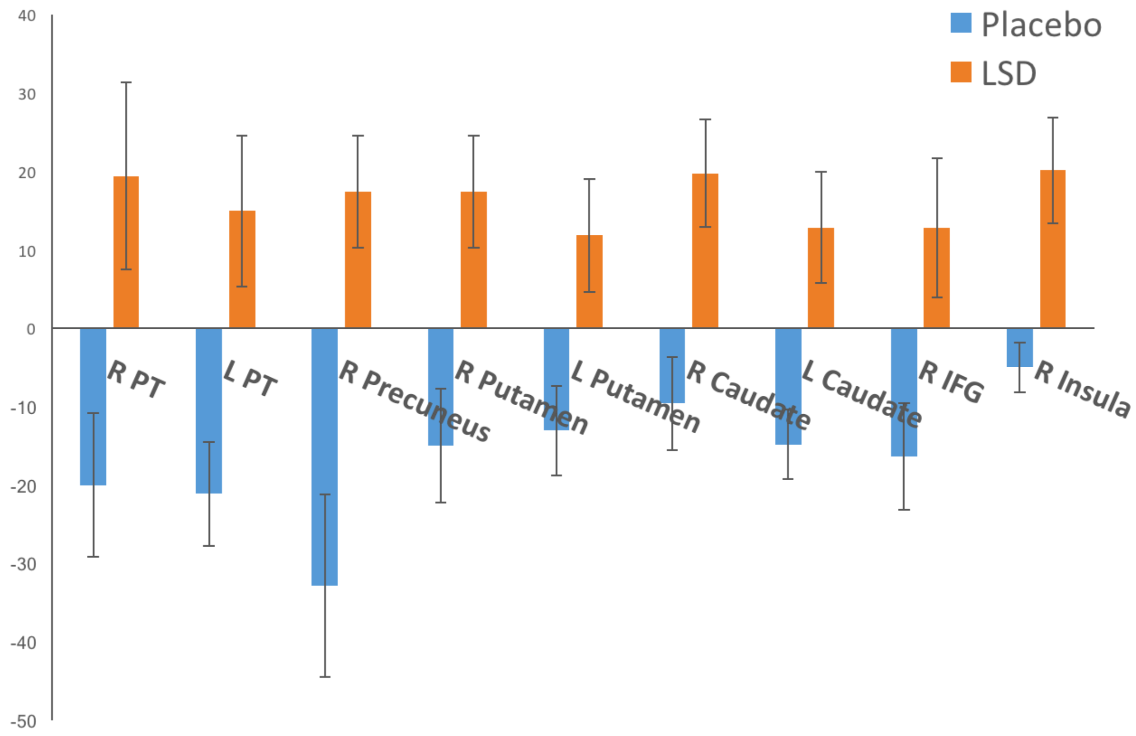

Figure 4.4 | BOLD activation to timbral complexity under placebo and LSD. The group average parameter estimates + standard error of the mean (Z-scores, displayed on the y-axis) for nine regions of interest (ROIs) (displayed on the x-axis), for placebo (blue) and LSD (red).

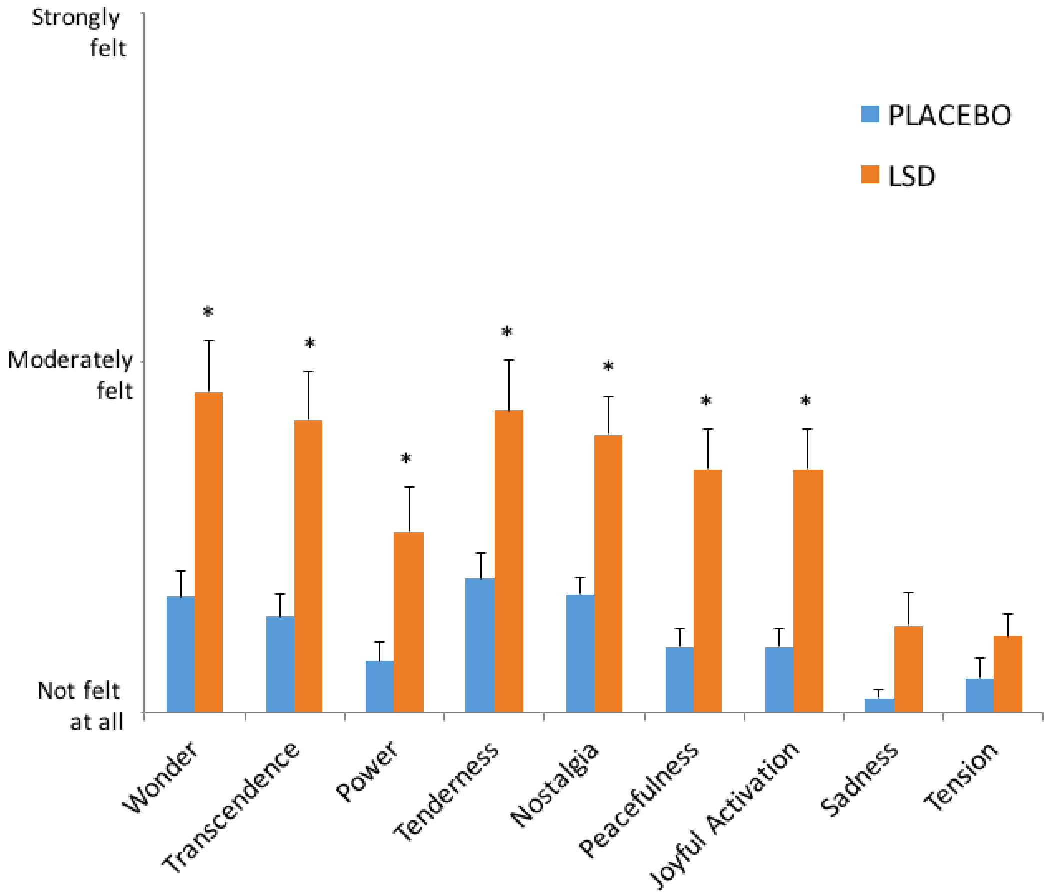

Figure 4.5 | Effects of LSD on music-evoked emotion. The average scores + standard error of the mean for each condition (placebo and LSD) for the nine music-evoked emotions assessed with the 25-item Geneva Emotional Music Scale (GEMS). Asterisks indicate a statistically significant finding ($p<0.05$) after multiple comparison correction.

4.3.4 Correlation analyses between music-evoked brain activity and emotion

Having established that psychedelics intensify the emotional experience with music, we subsequently focused exploring the interactions between peak experience emotions (as captured by the GEMS scales *wonder* and *transcendence* (Maslow, 1964, 1971; Zentner et al., 2008) and associated increases in music-evoked brain activity. We therefore conducted correlation analyses (Spearman's rank) between changes in music-evoked peak emotions (LSD > Placebo) and music-evoked BOLD activity (LSD > Placebo) for nine regions of interest (ROIs). This correlation analysis was constrained to the contrast for timbral complexity (i.e., PC3) as related BOLD changes were most pronounced and occurred in brain networks commonly identified for music perception and emotion (Koelsch 2014; Alluri et al., 2012). ROI selection was based on previous literature and encompassed structures that have been commonly identified for music-evoked emotion (striatum, precuneus and insula) (Trost et al., 2012; Koelsch 2014), auditory perception (planum temporale and right IFG) (Griffiths and Warren 2002b; Alluri et al., 2013, 2012; Zatorre and Salimpoor, 2013) and the subjective effects of psychedelics (precuneus and insula) (Muthukumaraswamy et al., 2013; Tagliazucchi et al., 2016; Carhart-Harris et al., 2016). See table 4.3 for the coordinates and size of each ROI. We found significant positive correlations between changes in music-evoked feelings of *wonder* and music-evoked BOLD activation to timbral complexity within the precuneus (r = 0.67, p = .034) as well as within the right inferior frontal gyrus (r = 0.65, p = .045) (see Figure 4.6). In addition, we found trend-level positive correlations between changes in feelings of *transcendence* and the right inferior frontal gyrus (r = 0.61, p = .066). P-values reported were corrected for multiple comparisons using one-sided permutation testing with α set to .05.

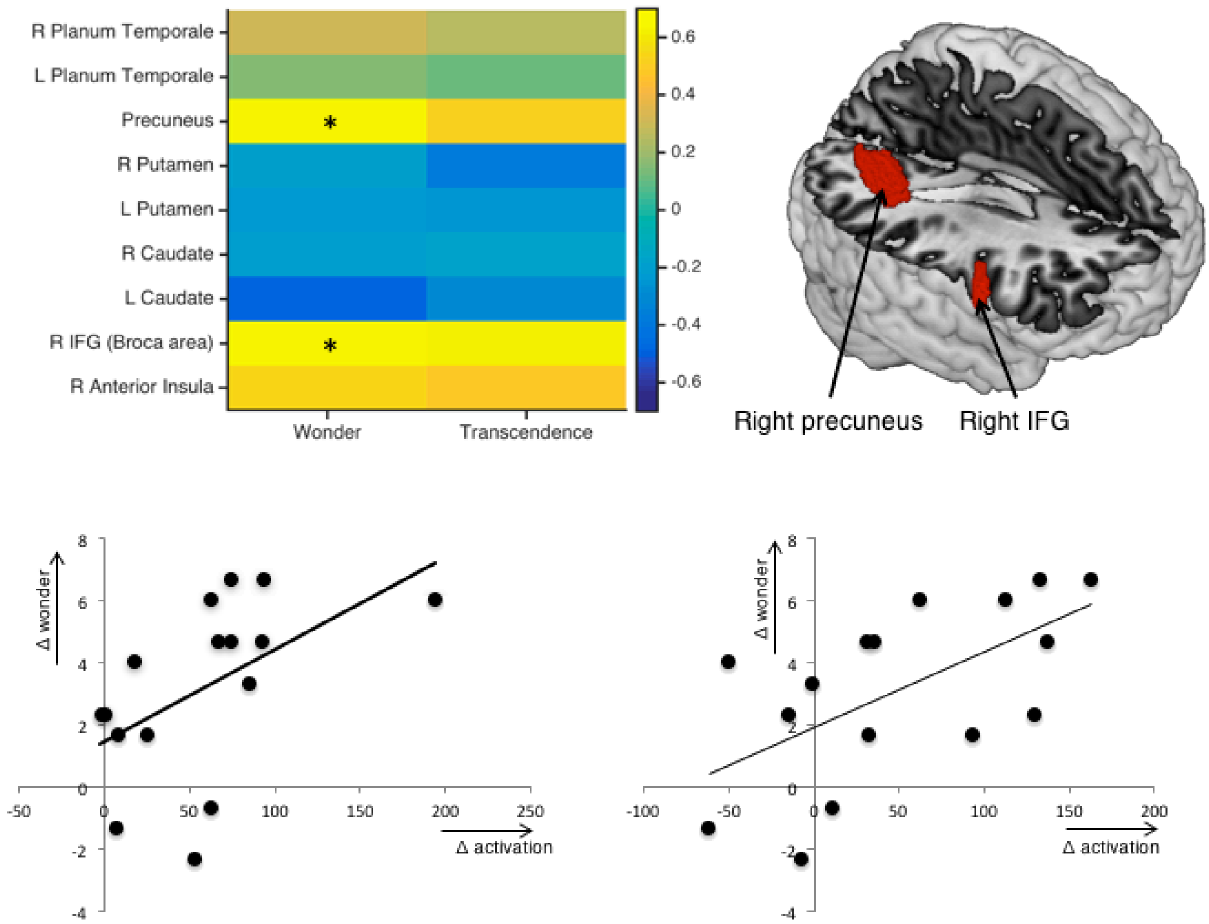

Figure 4.6 | Results from correlation analysis. **A)** Correlation matrix of parameter estimates with music-evoked peak emotions: wonder and transcendence. Asteriks indicate a statistically significant correlation (p ≤ 0.05) after multiple comparison correction. **B)** Location of masks for the right precuneus and right inferior frontal gyrus (IFG). **C)** Correlation plot showing a positive correlation between changes in parameter estimates in right precuneus and increases in music-evoked emotions of wonder under LSD (r = 0.67, p = .034). **D)** Correlation plot showing a positive correlation between changes in parameter estimates in the right inferior frontal gyrus and increases (difference between scores for LSD and scores for placebo, calculated as LSD minus placebo) in music-evoked emotions of wonder under LSD (r = 0.65, p = .045).

Table 4.3 | MNI coordinates for the centres of gravity of the ROIs (L = left, R = right).

Region	Coordinates (X,Y Z)			# voxels
R Planum Temporale	54.8	-22.6	11	290
L Planum Temporale	-48.8	-33	15.2	658
Precuneus	14.6	-62.6	19	414
R Putamen	22.8	10.2	-0.4	308
L Putamen	-25.6	1.4	3.8	364
R Caudate	15.2	14	8	158
L Caudate	-14.2	17.8	3.4	76
R IFG (Broca area)	58.8	9.8	14.6	60
R Anterior Insula	31.2	13.8	9	48

4.3.5 Effects of LSD and music on functional connectivity

The relationship between feelings of wonder and music-evoked activation to timbral complexity in the precuneus and the right IFG informed subsequent PPI analyses with the aim to gain insights into underlying music-specific changes in functional connectivity under LSD. Two separate PPI analyses were conducted, using either precuneus or right IFG as seed ROI, in order to identify brain areas for which the activation time course during the LSD condition were more (increased) or less (decreased) coupled with the seed regions depending on the level of timbral complexity in the music. Under LSD, we found significantly increased coupling of the precuneus with the right superior frontal gyrus (SFG) for passages when the music exhibited high timbral complexity. In addition, we found significantly decreased coupling of the precuneus with the right IFG as well as the right auditory cortex under LSD when timbral complexity in the music increased. No significant timbral-specific changes in functional connectivity were found for the right IFG as seed (Figure 4.7).

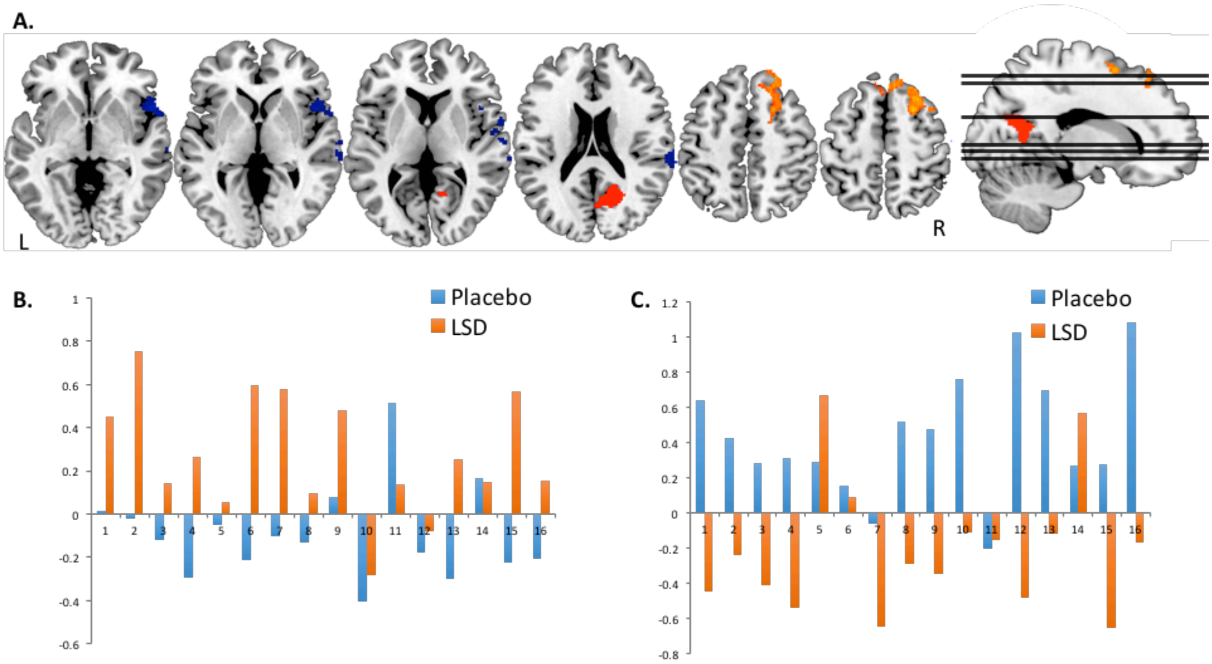

Figure 4.7 | Brain regions showing altered timbral-specific functional connectivity under LSD. A). Group level results from the PPI analysis using the right precuneus ROI (displayed in red). Increased coupling was observed in the right superior frontal gyrus, and decreases were observed in the right auditory cortex and right inferior frontal gyrus. Increases (LSD>placebo) are displayed in yellow, and decreases (placebo>LSD) are displayed in blue. Z < 2.3. B) Connectivity values of each individual participant and for each condition for the precuneus with the right superior frontal gyrus, and C) for the precuneus with the right inferior frontal gyrus and auditory cortex

4.3.6 Effects of head motion

In order to investigate the effect of motion on our results, frame-wise displacement (FD) was investigated between the drug and placebo condition as well as conducted correlation analyses between changes in FD (LSD>placebo) and extracted parameter estimates from the nine ROIs. The mean ± SD FD for placebo and LSD were 0.091 ± 0.037 and 0.174 ±0.1, respectively, which was found to be statistically significant using a paired t-test ($t_{(15)} = -3.28$, p=0.005). However, no significant correlations (Spearman's rank) was found between changes in FD (LSD>Placebo) and changes in music-evoked BOLD activity for the contrast timbral complexity (LSD > Placebo) in any of the nine ROIs: right planum temporale (r=0.04, p=0.88), left planum temporale (r=-0.01, p=0.97), precuneus (r=0.02, p=0.93), right putamen (r=-0.29, p=0.27), left putamen (r=-0.21, p=0.42), right caudate (r=-0.2, p=0.45), left caudate (r=-0.28, p=0.3), right IFG (r=0.29, p=0.27) and right insula (r=0.28, p=0.28). It can therefore be concluded that the effect of motion for our results seem negligible. P-values reported here are uncorrected for multiple comparisons. In addition, to control for an effect of FD on timbral complecity-evoked brain-activity, average FD for stimulus A and stimulus B were correlated with respective time-courses for timbral complexity, and no significant correlations were detected (*r=0.11, p=0.09, df=25* (stimulus A); *r=0.12, p=0.07, df=215* (stimulus B)).

4.4 Discussion

This study investigated the effects of LSD on the brain's processing of distinct acoustic features in music, and the relationship of these effects to changes in music-evoked emotion under LSD. Widespread BOLD activity changes were observed under LSD in cortical and subcortical areas to different acoustic features in the music. The BOLD signal increases observed under LSD to the component timbral complexity were found to be particularly meaningful, as the regions appear to lie within brain networks commonly identified for music-perception and music-evoked emotion. These include bilateral auditory cortices, right inferior frontal gyrus (IFG), right insula, precuneus, bilateral striatum and supplementary motor area (SMA). Music-evoked emotions were rated higher under LSD, and increased feelings of wonder correlated with increased BOLD activation to timbral complexity in the right precuneus and in the right IFG. Reduced functional connectivity under LSD in relation to timbral complexity was found between the right precuneus and auditory regions, and the right IFG. Increased functional connectivity under LSD in relation to timbral complexity was found between the right precuneus and the superior frontal gyrus (SFG). These findings invite us to discuss some of the following key questions: Why does LSD produced such marked changes in the way the brain processes timbre, also known as tone colour? And what are the possible brain mechanisms at stake? In the subsequent paragraphs, this will be discussed in light of previous neuroscience research, and of the significance of timbre for music-evoked emotion.

Timbre, or tone colour, refers to the properties of the sound distinct for pitch or loudness. Timbral complexity, in turn, corresponds to the complexity in the shape and the spread of music's spectral distribution. Thus, timbral complexity, can be treated as an index for the complexity in the shape of power spectrum of the sound signal. Spectral properties of sound are initially processed by the planum temporale (Kumar et al., 2007), a central "computational hub" within the auditory cortex that segregates incoming spectral signals into distinct spectrotemporal patterns (Griffiths and Warren, 2002b). Subsequent information exchange with higher cortical regions such as the IFG, is thought to facilitate the linking of the perceived spectrotemporal patterns with learned representations and associations (Zatorre and Salimpoor, 2013; Hackett, 2011). The auditory cortex and IFG are anatomically (Plakke and Romanski, 2014) and functionally (Tomasi and Volkow, 2012) well-connected, and considered an important pathway for the perception of auditory objects (Griffiths and Warren 2004; Zatorre and Salimpoor, 2013), musical melody (Zatorre et al., 1994), musical harmony (Schönwiesner et al., 2007; Opitz et al., 2002), musical syntax (Koelsch et al., 2002), and the encoding of musical expectation (Osnes et al., 2012; Zatorre, 2015) as well as musical imagination (Herholz et al., 2012). Damage and abnormal functioning in the auditory-IFG network has been linked to impaired music perception (Hyde et al., 2007; Hyde et al., 2011; Leveque et al., 2016) and auditory hallucinations (Looijestijn et al., 2013). The findings of the present study indicate that LSD has major effects on the way's the brain processes music's timbre properties, and it seems plausible that this effect relates to changes in auditory perception under psychedelics that are often reported (such as in the opening quote of this chapter), but this remains yet to be determined experimentally.

This experiment focussed on relating changes in brain function to changes in music-evoked emotion under LSD. Apart from a key role in music perception, converging evidence describes the IFG's involvement in the evaluation of emotional valence in acoustic information more generally. Happy emotional vocalisations produce increased IFG activity compared to angry vocalisations (Schirmer and Kotz, 2006; Wiethoff et al., 2008; Frühholz et al., 2016) - an effect that has been observed as early as 7-months in human infants (Grossmann et al., 2010). Brain damage and experimentally disrupting brain activity in the IFG using transcranial magentic stimulation (TMS), is linked with impairments in identifying vocal emotion (Hoekert et al., 2010). The IFG processes emotionally salient information from different sensory modalities (Lee and Siegle, 2012), and has been more generally conceptualised as being part of a cognitive control network (Marklund and Persson, 2012; Irlbacher et al., 2014) that redistributes attentional resources for emotionally salient information (Vuilleumier, 2005). Paying attention to the emotional valence of visual (Critchley et al., 2000; Schindler and Kissler, 2016) and auditory (Bach et al., 2008) stimuli is associated with increases in IFG activity, and emotionally salient information can produce marked attentional biases (Vuilleumier, 2005). Increased right IFG activation to music's timbral complexity under LSD, and the positive corelation with music-evoked 'peak' emotion, may therefore indicate increased allocation of attentional resources for emotional information processed within the auditory-IFG circuitry.

This view, that the auditory-IFG network may play an important role in LSD's effects on musical information processing, was further supported from the findings of the functional connectivity analyses. The PPI analysis revealed a significant decoupling between the right precuneus and the right auditory cortex and right IFG under LSD, in interaction with timbral complexity. The precuneus is a highly connected hub region that plays an important role in self-referential cognition (Buckner et al., 2008; Cavanna and Trimble, 2006) and emotion-regulation (Schilbach et al., 2012; Cavanna and Trimble, 2006), and shows desynchronized activity under psychedelics (Carhart-Harris et al., 2016; Muthukumaraswamy et al., 2013; Riba et al., 2002). This disorganising effect of psychedelics on precuneus activity has been associated with "ego-dissolution", characterised by increased emotional liability (Carhart-Harris et al., 2016; Tagliazucchi et al., 2014, 2016; Lebedev et al., 2015). Although the precuneus is activated to music-evoked emotion (Trost et al., 2012; Koelsch 2014;

Baumgartner et al., 2006), the region shows poor anatomical (Cavanna and Trimble, 2006) and resting state functional connectivity (Tomasi and Volkow, 2012) with auditory regions. The precuneus is however anatomically and functionally well-connected with frontal regions such as the IFG and SFG (Zhang and Li, 2012), and is thought to provide top-down control to these (hierarchically subordinate) brain regions (Cavanna and Trimble, 2006). As such, decreased precuneus-auditory/IFG coupling under LSD may reflect a reduced regulatory influence of the precuneus over emotion processing in the auditory/IFG network, and this may facilitate an intensified (or disinhibited) emotional response to music.

Finally, LSD also produced marked increases in BOLD activation to timbral complexity in the striatum and in the insula; regions that have been consistently associated with music-evoked emotion. The striatum has been implicated in brain mechanisms underlying music-evoked pleasure (Blood and Zatorre 2001; Salimpoor et al., 2011), likely via the encoding of auditory expectation and reward in interaction with auditory cortices (Salimpoor et al., 2015, 2013). The insula is a high-level hub region that is thought to facilitate emotional awareness (Craig 2009), the attribution of emotional meaning to music, sound and human voice (McGettigan et al., 2013; Frühholz et al., 2016; Petrini et al., 2011; Trost et al., 2012; Koelsch 2014), and the subjective effects of classic psychedelics (Carhart-Harris et al., 2016; Tagliazucchi et al., 2014, 2016; Lebedev et al., 2015). Interestingly, the present study did not find a relationship between music-evoked feelings of wonder and transcendence, and the striatum. An implication of this could be that the striatum is predominantly concerned with the processing of "simple" affective states characterised by pleasure, whereas more complex emotional states, such as feelings of wonder and transcendence, may require more complex cognition, and thus more complex cortical mechanisms to facilitate them. The selective positive correlation between increased feelings of wonder and BOLD signal changes in higher-level brain regions such the IFG and precuneus support this idea.

Taken together, these observations suggest that LSD alters the dynamic interplay between the analysis of "low-level" spectral properties in the music, and the subsequent "high-level" regulation and processing of the emotional associations. The precuneus, the IFG and the insula may play a particular important role in facilitating music-evoked peak emotion, given previous literature implicating their involvement in the processing of emotional awareness (Craig, 2009) and "complex" music-evoked emotion (McGettigan et al., 2013; Frühholz et al., 2016; Petrini et al., 2011; Trost et al., 2012; Koelsch 2014). A disintegration or weakening of the mechanisms that normally regulate emotion (Tagliazucchi et al., 2016; Lebedev et al., 2015), may be a fundamental mechanism via which strong emotional experiences with music can be facilitated under psychedelics. Discussing the possible brain mechanisms will be the focus of the subsequent paragraph.

4.4.1 Possible brain mechanisms

Classic psychedelics such as LSD stimulate serotonin 2A receptors (Kometer et al., 2013; Riga et al., 2016; Titeler et al., 1988a), which are primarily expressed on deep layer V pyramidal cells (Celada et al., 2013). Upon activation of these receptors, the cells' membranes depolarize, reducing the neuron's threshold for firing (Andrade 2011). Hyper-activation of the serotonin 2A receptor underlies desynchronised activity within high-level brain networks (Muthukumaraswamy et al., 2013), leading to impaired top-down control and an increased information exchange between brain modules that are usually more strictly functionally segregated (Tagliazucchi et al., 2016; Carhart-Harris et al., 2016). Deep layer V pyramidal cells encode learned mental representations or "predictions" that are matched with incoming sensory stimuli in a top-down fashion (Bastos et al., 2012), and over-activation of the serotonin 2A receptor system by psychedelics is reasoned to produce a disorganised or "entropic" quality of brain activity, manifesting as a more variegated quality of consciousness (Carhart-Harris et al., 2014).

The high density of serotonin 2A receptors within the precuneus, insula and the planum temporale (Ettrup et al., 2014; Erritzoe et al., 2009) suggests that psychedelics alter auditory information processing at different stages of the processing hierarchy. Since the planum temporale is functionally specialised in classifying distinct spectrotemporal patterns (Griffiths and Warren, 2002b), the particularly pronounced BOLD increases under LSD to "timbral complexity" in this region may reflect an increased activation of intrinsic deep-pyramidal neurons that encode (predictions for) music's spectral properties. Such an effect may result in dramatic alterations in the processing and perception of auditory spectral information (i.e. timbral complexity) in music, and thereby indirectly lead to an intensification of the emotional meanings that are conveyed through timbre.

Alternative to this hypothesis that holds LSD changes timbre-perception, is the view that increased activity in planum temporale may be consequential of an increased input from top-down projecting deep layer V pyramidal cells, originating from the IFG and insula and encoding emotional valence of timbre (McGettigan et al., 2013; Frühholz et al., 2016; Petrini et al., 2011; Trost et al., 2012; Koelsch 2014), i.e. an increased IFG/insula to planum temporale effective connectivity. Effective connectivity has not been assessed in this study, but doing so would aid testing such mechanistic hypotheses of LSD's effects on timbre-processing. Finally, one other possible brain mechanism at play could be that the decoupling of the auditory/IFG circuitry from the precuneus propagates an unregulated activation of timbre-emotion associations. The absence of this top-down control, would hence produce an intensified (disinhibited) emotional response to the emotions conveyed through music.

4.4.2 The significance of timbre

An important question is *why did LSD have such a marked effect specifically on the brain's processing of music's timbral complexity*? One explanation may be found in the significance of timbre in acoustic communication across species. Timbre is used across species to communicate salient information such as the presence of predators or the fitness of potential mates (Fitch, 1997; Bregman et al., 2016), and the perception of timbre is argued to have underwent high evolutionary selection pressure. Timbre's capacity to convey emotion is shown cross-culturally (Egermann et al., 2015), to do so independently from other acoustic features (Hailstone et al., 2009), and timbre-perception is present in very early infancy before the perception of other acoustic features develop, such as tempo and musical mode, and long before the acquisition of verbal language (Dalla Bella et al., 2001). The infants' ability to memorise and recognize their mother's voice as early as at 2 days after birth has been argued to be due the infant's innate tuning to timbral properties common to speech and music (Tsang and Trainor, 2002). Timbre has been conceptualised to function like an interface, that connects distinctive spectral features within sound with meaningful emotional associations (Hailstone et al., 2009). The findings of this study suggest that LSD targets this interface, "tuning" the brain to non-verbal, or even pre-verbal, acoustic properties that carry important emotional information.

4.4.3 Effects of LSD on the brain's processing of other acoustic features

The previous discussion centred around the changes observed for timbral-complexity, because these changes were most pronounced and appeared to be localised in networks commonly associated with music-perception and music-evoked emotion. However, there were other findings that must be mentioned. Increased thalamus and decreased IFG activation was observed under LSD in response to "fullness", i.e. simply the loudness of the sound. Loudness reflects a less complex acoustic property (occupying a single dimension, i.e. amplitude of the signal), and has previously been associated with a preferential activation of lower auditory regions (Reiterer et al., 2007). Significant BOLD signal changes were also observed in occipital cortices for various acoustic features, an area rich in serotonin 2A receptors and significantly functionally altered under LSD alone (Roseman et al., 2016).

4.4.4 Implications for psychedelic therapy

The present study supports the usefulness of music in facilitating peak experience, which are associated with positive therapy outcomes (Garcia-Romeu et al., 2014; Griffiths et al., 2016; Ross et al., 2016). The findings also suggest that knowledge on how timbre conveys emotion, may be a particular fruitful avenue to inform music-selection for psychedelic therapy.

4.4.5 Study limitations and future directions

The study focussed on LSD's effects on the neurophysiological processing of acoustic properties in music, but did not included perceptual measures for these features. Future studies may address questions such as "is timbre perceived differently?", and "are certain acoustic features experienced more differently than other features?". Studies assessing these questions will be in particular important for our understanding of how psychedelics alter the perception of music, how this relates to changes in music-evoked emotion, and more broadly, in how understand and use music in psychedelic herapy.

Another study limitation was that only a single musical genre was used. The music used was rich in timbre, but low in tempo. The music choice may therefore have resulted in a selective reflection of LSD's effect on timbral features in music, since it can be hypothesised that other brain networks will be engaged when, for example, more rhythmic music is used. However, the component for which LSD showed most pronounced neurophysiological changes (i.e. "timbral complexity"), was not the component that explained most of the variance within the music (i.e. being the third component), supporting the validity of the method in identifying brain changes to distinct and diverse musical features within a naturalist music listening experience.

4.4.6 Conclusions

The present study revealed altered brain activity and connectivity to acoustic features in music under LSD. Most pronounced changes were observed for the component timbral complexity, representing the complexity of the music's spectral distribution, and these occurred in brain networks previously identified for music-perception and music-evoked emotion. These changes showed a correlation with enhanced music-evoked feelings of wonder under LSD. The findings suggest music can be utilised in psychedelic therapy to facilitate peak experiences, and provided insights into the brain processes underlying music perception and peak emotion under naturalistic listening conditions.

“The reactions music evokes are not feelings, but they are the images, memories of feelings. Dreams, memories, musical reactions - all three are made of the same stuff”

Paul Hindemith

5 *Study 3* | Effects of LSD and music on parahippocampus connectivity and mental imagery

5.1 Background

Albert Hofmann described his first experience with LSD, in his memoir *LSD, my problem child.* He wrote:

> "It was particularly remarkable how every acoustic perception, such as the sound of a door handle or a passing automobile, became transformed into optical perceptions. Every sound generated a vividly changing image, with its own consistent form and colour." (Hofmann, 1980)

This experience was also the first experience with LSD in modern history, and it already captured a feature of psychedelics' subjective effects that became a great fascination for scientists, artists and therapists: the combined effects of music and psychedelics on visual mental imagery. Since the inception of psychedelic therapy, it is thought that music acts synergistically with the drug to stimulate the imagination in idiosyncratic and powerful ways: to evoke mental images, memories and thoughts that are highly vivid and have significant personal meaning (Bonny and Pahnke 1972; Grof, 1980). The focus of study 2 was on the effects of LSD on music-evoked emotion, yet it was striking to us how frequently participants elaborated on the ways music influenced their "extremely vivid" eyes-closed mental imagery, such as in this remark on the music-experience:

> “The imagery was quite strong. And I felt quite present in the imagery. In the beginning, I felt like I was in a ditch, a muddy ditch, then, like a sort of faded vision or photograph, I felt like I was on a rock, a version of a planet, and I was revolving around it and I then flew into space. And then I had clear images of my daughter, and this was very moving. There was a sense of mortality, and the music kind of forced me to have a larger perspective. I saw specific images, and with strong emotions.”

And another participant recalled:

> “There were lots of memories of home, and lots of memories and thoughts of my own family. […] It was like the soundtrack of a film, a little trailer of a film.”

The main aim of this study was to investigate this phenomenon empirically, by studying brain mechanisms underlying the effects of LSD and music on mental imagery. Of particular interest to the neuro-scientific study of mental imagery is the parahippocampal cortex (PHC). The PHC is an important hub within the medial temporal lobe (MTL) system (Burwell 2000; Eichenbaum and Lipton 2008), and plays a role in constructing mental imagery (Spreng et al., 2009; Zeidman et al., 2014) and autobiographical memory recall (Fink et al., 1996). Damage to the PHC can result in visual deficits (Harding, Broe, and Halliday 2002; Hensley-Judge et al., 2013), whereas direct stimulation of the PHC can produce visual hallucinations of scenes (Mégevand et al., 2014), vivid autobiographical memories (Vignal et al., 2007) and dream-like states (Bancaud et al., 1994; Bartolomei et al., 2004), accompanied by enhanced coupling between the PHC and the visual cortex (VC) (Barbeau et al., 2005).

Importantly, PHC activity is modulated by music and psychedelics separately. The PHC receives direct projections from the auditory cortex (Amaral et al., 1983), and shows increased activity during music-evoked emotion (Gosselin et al., 2006; Koelsch 2014) and music-evoked personal memories (Janata 2009). The PHC expresses serotonin 2A receptors (Pazos, Probst, and Palacios 1987), and altered PHC functioning under psychedelics has been observed using fMR (Tagliazucchi et al., 2014), depth EEG (Monroe et al., 1957; Schwarz, Sem-Jacobsen, CW, and Petersen, MC 1956) and PET (Vollenweider et al., 1997).

Furthermore, attenuation of the subjective and behavioural effects of LSD were observed after resection of the MTLs in humans (Serafetinides 1965) and chimpanzees (Ramey and O'Doherty, 1960), suggesting a role for the MTL in facilitating subjective effects of psychedelics.

These insights motivated the hypothesis that LSD in combination with music modulates PHC functional connectivity to enhance mental imagery. This hypothesis was tested using functional magnetic resonance imaging (fMRI) and a balanced-order, placebo-controlled design, with healthy participants. Measures for changes in PHC functional connectivity informed a subsequent Dynamic Causal modelling (DCM) analysis that assessed how an interaction effect between music and LSD modulates the direction of information flow between the PHC and the VC (i.e. effective connectivity). Participants completed ratings of eye-closed visual imagery and spontaneous recall autobiographical memories to assess subjective effects, which were correlated with changes in effective connectivity.

5.2 Methods

5.2.1 Approvals

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

5.2.2 Participants

Twenty participants (16 males and 4 females) were recruited, carefully screened for physical and mental health and provided written informed consent before participation. The screening for physical health included electrocardiogram (ECG), routine blood tests, and urine test for recent drug use and pregnancy. A psychiatric assessment was conducted and participants provided full disclosure of their drug use history. Key exclusion criteria included:

being younger than 21 years of age, having a personal history of diagnosed psychiatric illness, an immediate family history of a psychotic disorder, an absence of previous experience with a classic psychedelic drug (E.g. LSD, mescaline, psilocybin or dimethyltryptamine (DMT), drug use within 6 weeks of the first scanning day, a persistent adverse reaction to a psychedelic drug, pregnancy, problematic alcohol-use (i.e. > 40 units consumed per week), and/or a medically significant condition rendering them unsuitable for the study.

5.2.3 Experiment overview and procedures

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

On scanning days, volunteers arrived at the study centre at 8:00 am, were given a detailed brief 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. Participants were encouraged to close their eyes and relax in a reclined position while the drug was administered. All participants received 75 µg of LSD, administered intravenously via a 10 ml solution infused over a two minute period, followed by an infusion of saline. Dosing 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 prepare the participants for the subsequent (potentially anxiogenic (Studerus et al., 2012)) MRI scanning experience.

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. BOLD MRI scanning started approximately 120 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, magnetoencephalography (MEG) scanning was performed but these findings will be reported elsewhere. Once the subjective effects of LSD had sufficiently subsided, the study psychiatrist assessed the participant's suitability for discharge.

5.2.4 fMRI study design

Each fMRI scanning session involved three eyes-closed resting state scans, each lasting seven minutes. After each scan (7 minutes and 20 seconds), visual analogue scale (VAS) ratings were performed in the scanner via a response-box after each scanning block (no music, music, no music). The music-listening scan always occurred after the first resting state (no music) scan and before a final resting-state scan (no music). The music itself was triggered by the first TR, and listened to via MRI compatible headphones (MR Confon). Two long excerpts (A and B, each 7 minutes and 20 seconds in duration) were selected from the album Yearning, by musicians Robert Rich and Lisa Moskow. Pre-study assessments confirmed the two excerpts to be balanced for their emotional potency. Each participant listened to both stimuli, in a balanced order across conditions. Volume-maximization and broadband compression was carried out using Ableton live 9 software.

Prior to each scan, participants were instructed via a display screen to close their eyes and relax. Prior to the music scan, the music volume was adjusted to a level that was "as loud as possible, without being unpleasant" and then maintained for each condition. When the music ended, participants were instructed to open their eyes and rate the degree of simple mental visual imagery (i.e. "with my eyes closed I saw colours or geometric patterns") and complex mental visual imagery (i.e. "with my eyes closed I saw complex hallucinations") they experienced. Complex imagery was defined for the participants prior the scanning as the seeing of concrete objects, landscapes or entities (E.g. plants, buildings, people or animals). Items were completed on a continuous visual analogue scale from 0 ("not at all") to 20 ("extremely intense"). Soon after the MRI scanning session was complete, participants rated some further VAS items that assessed their subjective experience during scanning. The VAS item "I saw scenes from my past" was selected for special consideration because of personal memory recollection being consistently associated with PHC functioning (Fink et al., 1996;

Spreng et al., 2009), as well as a prior hypothesis inspired by previous findings (Carhart-Harris et al., 2012b) that this would be modulated by the experimental conditions.

5.2.5 fMRI scanning and data pre-processing

All imaging was performed on a 3T GE HDx system. For registration and segmentation of functional images, an initial 3D FSPGR anatomical scan was obtained in an axial orientation, with field of view = 256× 256× 192 and matrix = 256 × 256× 192 to yield 1-mm isotropic voxel resolution (TR/TE = 7.9/3.0 ms; inversion time = 450 ms; flip angle = 20°). Functional images were acquired using a gradient echo planer 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 BOLD scans was 7:20 minutes.

Pre-processing utilised a combination of AFNI (Cox, 1996), FSL (Smith et al., 2004b), Freesurfer (Dale et al., 1999) and ANTS (Avants et al., 2011). After brain extraction (Freesurfer), anatomical images were segmented into their three underlying tissue types: cerebrospinal fluid (CSF), grey matter (GM) and white matter (WM) (fast, FSL) and registered to a 2mm MNI152 template using affine (ANTS), followed by non-linear transformation (SyN, ANTS). Anatomical images also underwent segmentation to define subcortical structures (Freesurfer).

Participants in this study were from the same experiment as study 2, but due differences in the measures used in the separate studies, different inclusion criteria were used for data-analyses (connectivity measures here versus BOLD activition in study 2). One participant was excluded from analyses because of early termination of the scanning due to him reporting significant anxiety during the LSD session. Three participants were excluded from analyses due to technical problems with the sound delivery and four more subjects were discarded from the group analyses due to excessive head movement. This leaves a total of twelve participants that entered the group analyses. Principally, motion was measured using frame-wise displacement (FD) (Power et al., 2014). The criterion for exclusion for excessive head movement was subjects displaying higher than 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 0.286±0.185 and for the 12 subjects that were used in the analysis the difference in mean FD was 0.049 ±0.029 (mean FD for placebo was 0.085 ±0.028 and mean FD for LSD was 0.134 ±0.037, p = 0.0001).

Functional images were pre-processed according to the following sequence: 1) Removal of first three volumes 2) de-spiking (3dDespike, AFNI),3) slice time correction (3dTshift, AFNI), 4) motion correction (3dvolreg, AFNI), 5) brain extraction (bet, FSL), 6) rigid body registration to anatomical scans (nine subjects with FSL's BBR, one subject with Freesurfer's bbregister and two subjects manually) , 7) transformation of functional to MNI 2mm space, using previously calculated transformation matrix from the anatomical scans, 8) motion scrubbing using an FD threshold of 0.4, and replacement with the mean of neighbouring volumes (mean percentage of volumes scrubbed for placebo and for LSD was 0.5% ±1 and 1.9% ±2.2, respectively. Maximum volumes scrubbed for scan was 7.8%), 9) spatial smoothing with a Gaussian kernel of 6mm (FWHM) (3dBlurInMask, AFNI), 10) band-pass filtering between 0.01 to 0.08 Hz (3dFourier, AFNI) 11) linear and quadratic de-trending and regression of 9 nuisance parameters: 6 motion-related (3 translations, 3 rotations) and 3 anatomically-defined.

The anatomically defined regressors consisted of Ventricles (Freesurfer), Cerebrospinal fluid (CSF) (FSL's FAST with Freesurfer's Ventricles subtracted) and White matter (WM) (FSL's FAST with Freesurfer's subcortical grey-matter subtracted). All three masks were eroded to reduce partial volume effects and were used to extract nuisance timeseries from an unsmoothed version of the pre-processed functional data. The CSF and Venticles were used to extract a single mean time-course for each mask, while WM mask was used to produce a voxelwise regressor (3dLocalStat, AFNI). Voxelwise WM regression has been found to outperform approaches using whole-brain averaged WM signal (Jo et al., 2010, 2013).

5.2.6 Subjective effects

A two-way repeated measures ANOVA with two factors (drug condition and music condition) was performed to test for an interaction between LSD and music on in-scanner ratings of simple and complex visual imagery. A paired one-tailed t-test was performed to examine between-condition differences in the post-scanner questionnaire item “I saw scenes from my past”.

5.2.7 Seed-based functional connectivity analysis

A bilateral PHC region of interest (ROI) was acquired from the Harvard anatomical atlas tool and used to extract PHC time series for each subject. To begin with, a general linear model (GLM) was used (FEAT, FSL) to model whole brain resting state functional connectivity with the PHC seed, with correction for autocorrelations (FILM, FSL) for each run separately. Next, a fixed-effects model was used to compare music versus non-music runs for each subject, for LSD and placebo separately. Finally, these drug effects (LSD versus placebo) were fed into a higher-level mixed effects model (FLAME1, FSL) to calculate the modulation of the effects of music by LSD on PHC functional connectivity across the brain (cluster correction threshold $z > 2.3$, $p < 0.05$).

5.2.8 Dynamic Causal Modelling: Background and implementation

Dynamic Causal Modelling (DCM, as implemented in SPM12b) was used to estimate changes in effective connectivity. DCM is a biologically-informed modelling procedure that estimates the causal interactions (i.e. effective connectivity) between different pre-selected nodes of a network, and the changes in coupling strength between and within those nodes (extrinsic and intrinsic connections respectively) due to experimental manipulations (Friston et al., 2003). The basic architecture of a model is defined by structurally plausible and functionally-informed brain regions, whose connections are defined as either bilinear (i.e. information flow between regions) or non-linear (i.e. activity in one region modulating information flow between regions). Typically, experimental manipulations can directly affect activity in each node (as ‘driving inputs’) or alter the strength of coupling within or between nodes (as ‘modulatory inputs’).

In the present study, all six scans were concatenated in the following order: placebo no-music (NM), placebo music (M), placebo NM, LSD NM, LSD M, LSD NM. The measured BOLD time-series for the DCM were extracted as the first principal eigenvalue from a bilateral PHC and VC mask (The PHC mask was defined by Harvard-Oxford atlas, and the VC mask was defined by results of the PHC functional connectivity analysis, i.e. the occipital cluster), and adjusted for the effects of interest (i.e. main effect of music, main effect of drug, and an interaction effect - described below). Between-node connections were defined as bilinear meaning that information flow could be modulated in either direction. Three experimental inputs entered the model as modulatory inputs: a main drug effect, a main music effect, and an interaction effect of music and drug (0.5 -1 0.5 -0.5 1 -0.5). Due to the resting-state conditions of the scanning, activity in the nodes was driven by stochastic (i.e. spontaneous) fluctuations (Li et al., 2011).

5.2.9 Dynamic Causal Modelling: Bayesian Model Selection

In DCM, a series of plausible models, representing competing hypotheses, are specified. Each model corresponds to a hypothesis about how observed changes in BOLD signal were caused by changes in neural activity in each network node. The different models can vary in terms of the position of driving and modulatory inputs. DCM uses a biophysical model of the hemodynamic response to predict the underling neuronal activity – and the underlying (changes in) connectivity – from the observed BOLD signal. Model estimation, or inversion, returns conditional estimates for the changes in connectivity and scores the model in terms of its accuracy and complexity (using a Free Energy bound on log model evidence). Bayesian Model Selection (BMS) is used to compare different models to identify the model with the greatest evidence – i.e. the model that offers the best explanation of the data. In the present study, one “full model” was specified, with all three experimental inputs modulating all extrinsic and intrinsic connections. Following inversion of this full model, a post hoc Bayesian model optimisation scheme was used to identify the model structure with the greatest model evidence (i.e. lowest free energy). This approach provides an efficient scheme for scoring large numbers of competing models (Friston and Penny, 2011). Optimal model structure is usually determined by computing Bayes factors, as an approximation of the model evidence. A Bayes factor of 20 corresponds to a belief of 95% in the statement that a particular hypothesis (i.e. the proposed model) is true, and therefore a p value of 0.05. A Bayes factor higher than 150 corresponds to a belief of 99% in the hypothesis, and equates a p-value smaller than 0.01. A Bayes factor higher than 95 is therefore considered as strong evidence for the proposed model. After model selection, coupling parameters are analysed post-hoc to characterize the size and direction of the changes in connection strength caused by the experimental manipulations. Coupling parameters quantify the strength of the coupling in terms of the rate (in Hz) at which a response is caused in a given region, and modulation is expressed as either an increase or decrease in this coupling measure.

5.2.10 Correlation analyses between changes in effective connectivity and subjective effects

Following model selection, the hypothesis was tested that the magnitude of the modulation in effective connectivity by the music x drug interaction would explain the observed variance in participants' subjective responses to the music under LSD. More specifically, we asked whether the size of the interaction effect as estimated by the DCM, correlated with the magnitude of the enhancement of: 1) eyes-closed imagery and 2) visions of one's past ("I saw scenes from my past"). A spearman's correlation was used due the non-parametric nature of the data.

5.3 Results

5.3.1 Participants

The data from twelve participants were found suitable for data-analysis (2 female, mean age = 33±9 years, range 22-47 years). All had at least one previous experience with a classic psychedelic drug. Mean estimated lifetime LSD-use was 12 ± 15 (range = 0 - 40). Self-estimates of other drug-use were as follows (mean ± SD, range): weekly alcohol units = 8 ± 8, 0-28; daily cigarettes = 0; lifetime cannabis uses = 686 ± 625, 30-2000; lifetime MDMA uses = 20± 18, 2-50; lifetime psilocybin/magic mushroom uses = 10 ± 9, 1-35; lifetime ayahuasca/DMT uses = 14 ± 21, 0-50; lifetime ketamine uses = 3 ± 6, 0-20; lifetime cocaine uses = 6 ± 8, 0-20; lifetime amphetamine uses = 6 ± 11, 0-35; lifetime heroin uses = 1 ± 3, 0-10.

5.3.2 Subjective effects as measured by in-scanner ratings

A paired t-test revealed a significant increase in personal memory recollection under LSD ($t = 1.9$, $df = 19$, $p = 0.04$). For simple visual imagery, a two-way ANOVA revealed a significant drug effect ($F = 42.2$, $df = 18$, $p < 0.001$) but no significant effects were found for music ($F = 1.7$, $df = 18$, $p = 0.2$) or the interaction between music and LSD ($F = 1.1$, $df = 18$, $p = 0.3$). For complex visual imagery, a two-way ANOVA revealed a significant drug effect ($F = 24.7$, $df = 18$, $p < 0.001$), a trend level effect of music ($F = 10.0$, $df = 18$, $p = 0.09$), but again, no significant interaction effect for music x LSD ($F = 1.8$, $df = 18$, $p = 0.5$). Positive (enhanced) drug effects on simple and complex visual imagery survived multiple comparisons, using Bonferroni adjusted alpha levels of .025 per test (0.05/2) (see Figure 5.1).

5.3.4 Functional connectivity

Seed-based functional connectivity analysis of the bilateral PHC showed a positive interaction between music and LSD for the contrast LSD (music versus no music) versus placebo (music versus no music), with increased coupling between the PHC and two main clusters: One being the bilateral visual cortex and the other being the left inferior frontal gyrus and insula. No decreases in PHC functional connectivity were observed for this contrast. All effect reported are cluster-corrected, $Z>2.3$. (see Figure 5.2, for the reader's insight, other contrasts are displayed too).

5.3.5 Effective connectivity

Post-hoc model optimisation determined the optimal model structure. The optimal model had a Bayes factor 344 higher than the 2nd best model. This equates, in a frequentist statistical approach, to a p-value much smaller than 0.01, and is therefore considered as very strong evidence for the model. The optimal model features a main effect of drug and music modulating the intrinsic connections of both nodes, and an interaction effect modulating the connection from the PHC to the VC. Group averages for the posterior estimates are -0.41 ± 0.05 Hz for drug effect on PHC, -0.42 ± 0.06 Hz for music effect on PHC, -0.38 ± 0.06 Hz for drug effect on VC, and -0.40 ± 0.06 Hz for music effect on VC. The group average of the posterior estimate for the interaction effect is 0.02 ± 0.04 Hz (see Figure 5.3)

5.3.6 Correlations between changes in effective connectivity and subjective effects

A significant positive correlation was found between the interaction effect of LSD and music on PHC to VC effective connectivity, and increases in the in-scanner ratings for complex visual imagery (Spearman's ρ =0.71, with p=0.01, and Pearson r = 0.65, with p = 0.03). A trend-level positive correlation was found between the interaction effect of LSD and music on PHC to VC, and the post-scanner questionnaire item "I saw scenes from my past" (Spearman ρ =0.67, with p=0.02, and Pearson r = 0.69, with p =0.01). These tests were conducted using Bonferroni adjusted alpha levels of .0167 per test (0.05/3) (see Figure 5.4).

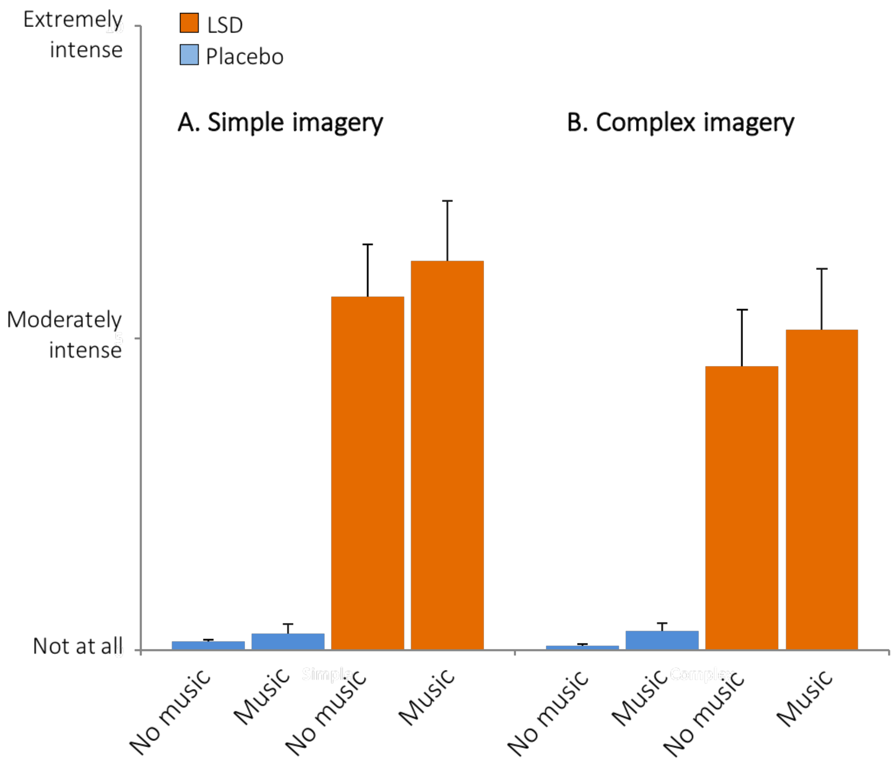

Figure 5.1 | Scanner-ratings for mental imagery. For simple visual imagery, a two-way ANOVA revealed a significant drug effect (F = 42.2, df = 18, p < 0.001) but no significant effects were found for music (F = 1.7, df = 18, p = 0.2) or the interaction between music and LSD (F = 1.1, df = 18, p = 0.3). For complex visual imagery, a two-way ANOVA revealed a significant drug effect (F = 24.7, df = 18, p < 0.001), a trend level effect of music (F =

10.0, df = 18, p = 0.09), but no significant interaction effect between music and LSD (F = 1.8, df = 18, p = 0.5). Drug effects on simple and complex imagery survived multiple comparisons, using Bonferroni adjusted alpha levels of .025 per test (0.05/2).

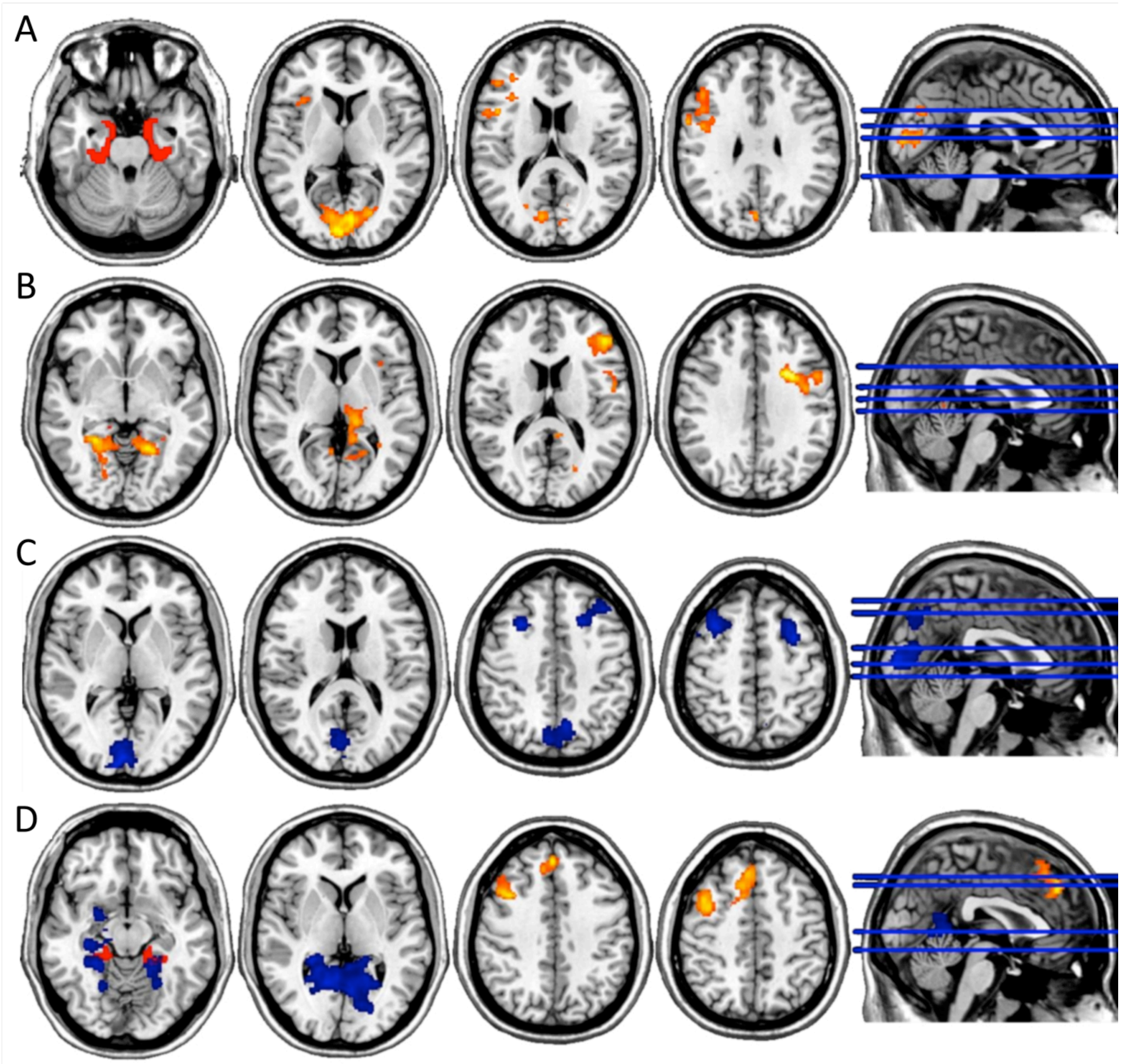

Figure 5.2 | Seed-based functional connectivity analysis of the bilateral parahippocampus. Brain regions showing increased coupling with the bilateral parahippocampus (PHC, displayed in red) are displayed in yellow, and brain regions showing decreased coupling with the bilateral PHC are displayed in blue (Cluster-corrected, Z>2.3). A) The contrast LSD (music > no music) > placebo (music > no music). No decreases were found. B) The effect of music under LSD (music > no music). No decreases were found. C) The effect of music under placebo PCB (no music > music). No increases were found. D) The effect LSD under resting state conditions (LSD (no music) > placebo (no music)) and (placebo (no music) > LSD (no music))

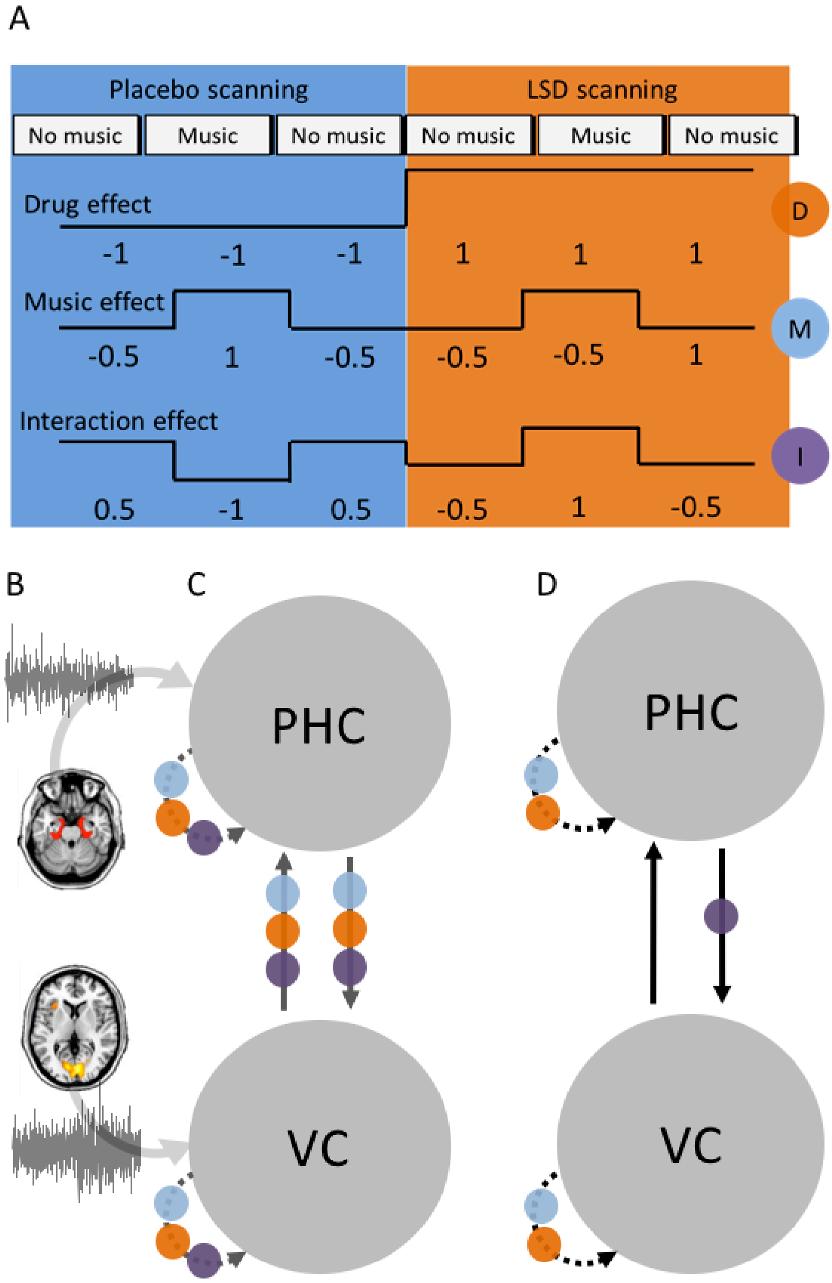

Figure 5.3 | Dynamic Causal Modelling. A) All scans are concatenated, and three effects of interest are modelled accordingly. D (red) = drug effect, M (blue) = music effect, I (purple) = interaction effect. B) Time series that enter the DCM are extracted as first principal eigenvalues from the PHC mask and the VC mask. C) The full DCM model has two nodes (PHC and VC) that are connected via extrinsic bilinear connections, and each node has one intrinsic connection. Every connection has all modulatory effects. D) Post-hoc model optimisation determined the optimal model structure. Dashed lines indicate a negative connection or modulation, whereas normal lines indicate a positive connection or modulation. This model has the main effect of drug and the main effect of music modulating the intrinsic-connections of both nodes. The interaction effect only has a modulatory effect on the connection from PHC to VC.

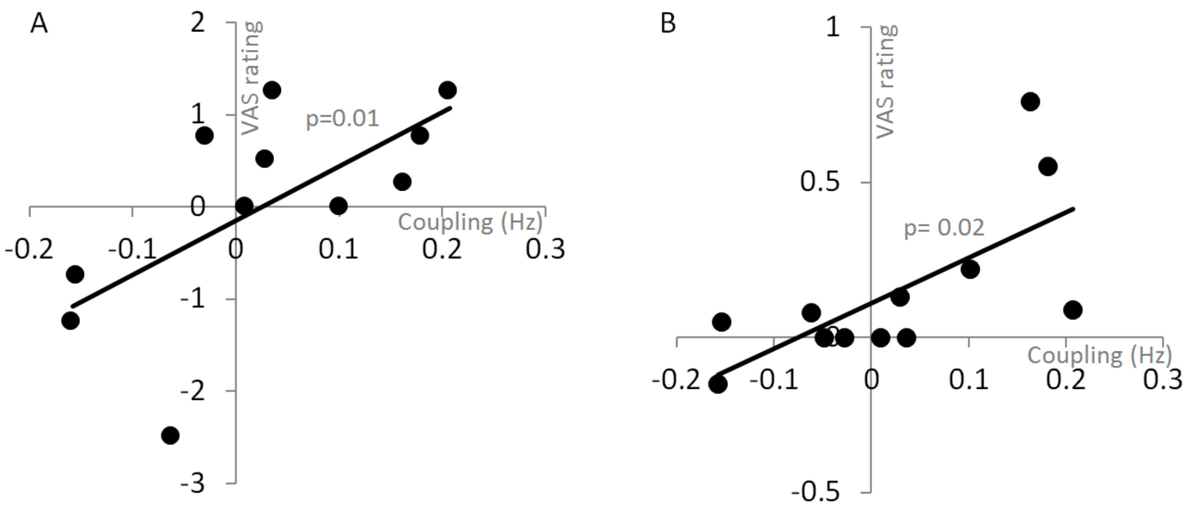

Figure 5.4 | Correlations between changes in effective connectivity and subjective effects. The correlation analyses revealed that the estimated modulation of PHC-to-VC effective connectivity (by Dynamic Causal Modelling), by the interaction between LSD and music, correlates positively with **A)** increased complex imagery (Spearman's ρ =0.71, with p=0.01, and Pearson r = 0.65, with p = 0.03)., and **B)** increases in visions of one's personal past (Spearman ρ =0.67, with p=0.02, and Pearson r = 0.69, with p =0.01). Changes in coupling parameters are displayed on the x-axis, and changes in subjective ratings are displayed on the y-axis.

5.4 Discussion

This study assessed neurophysiological changes associated with music-induced mental imagery under LSD. The results demonstrated increased functional connectivity of the parahippocampus (PHC) with the left inferior frontal gyrus (IFG), the left insula and the visual cortex (VC) during music listening under LSD. By using dynamic causal modelling (DCM), a positive modulation of effective connectivity (i.e. the direction of information flow) was found from the PHC to VC, by an interaction between the LSD and music. Furthermore, we found that the magnitude of this modulation correlated with increased ratings for eyes-closed complex visual imagery and personal memory recall.

These results are consistent with the converging view that the PHC-VC pathway serves as an important network for the (re)construction of mental images. The PHC is implicated in imagining scenes (Brewer et al., 1998; Spreng et al., 2009), episodic personal memory recollection (Fink et al., 1996; Spreng et al., 2009) and music-evoked personal memories (Janata 2009). The PHC and VC are structurally (Catani et al., 2002) and functionally (Libby et al., 2012; Powell et al., 2004) connected, and increased effective connectivity from the PHC to the VC has previously been associated with the construction of imagined visual scenes (Chadwick et al., 2013).

Of particular significance for the present findings, are studies in which the PHC was directly stimulated or damaged. Direct stimulation of the PHC has been found to produce hallucinations of complex visual scenes (Mégevand et al., 2014) and recall of autobiographical memories (Bancaud et al., 1994; Bartolomei et al., 2004). Furthermore, Barbeau et al (2005) demonstrated that upon direct stimulation of the PHC, a strengthening of PHC-VC coupling occurred only when such visual experiences were reported (Barbeau et al., 2005). Damage to the PHC can result in visual impairments (Hensley-Judge et al., 2013), visual hallucinations (Harding et al., 2002), and hippocampal damage has been associated to an impaired ability to imagine autobiographical past and future (Cooper et al., 2011)

Altogether, these studies provide a body of evidence that implicate the PHC-VC network as an important *mechanistic* pathway for the construction of mental visual images, whether this imagery is *real (*i.e. personal memories) or *imaginary* (Chadwick et al., 2013; Zeidman et al., 2014). And consistent with this view, the present findings suggest that psychedelics and music influence mental imagery by modulation of PHC-to-VC effective connectivity. Possible underlying mechanisms via which psychedelics and music may cause this modulatory influence will be proposed in the following section.

5.4.1 Possible brain mechanisms

The PHC can be subdivided into the perirhinal cortex, the postrhinal cortex and the entorhinal cortex (Burwell, 2000; Eichenbaum and Lipton, 2008; van Strien et al., 2009). The entorhinal cortex shows prominent bidirectional connectivity with the visual cortex (Morris et al., 1999), and receives direct input from the auditory cortex (Amaral et al., 1983). The PHC can be conceptualised as a central “hub”, an important relay station, that receives and integrates input from dispersed functionally specialised brain areas (Eichenbaum and Lipton, 2008).

The majority of axonal projection that the entorhinal cortex receives from the auditory cortex terminate on deep layer V pyramidal neurons (Mohedano-Moriano et al., 2007). These neurons express serotonin 2A receptors (Pazos, Probst, and Palacios 1987; Celada et al., 2013), and provide intra-hippocampal forward projections as well as backward projections to the visual cortex (Sewards and Sewards 2003). Because LSD increases excitability of deep layer V pyramidal neurons via serotonin 2A receptor activation (Aghajanian and Marek 1999), this leads to the prediction that under LSD the backward PHC-to-VC projections are more likely to fire in response to input from the auditory cortex.

In light of these studies, the findings of this study may indicate that under LSD, backward PHC-to-VC projecting pyramidal neurons in the PHC become abnormally engaged in response to music. An interesting analogy can be found in epileptic seizures, where abnormal activity of backward projecting pyramidal neurons within the MTL are hypothesised to be responsible for the seizures, and the entorhinal cortex is found to be in particular susceptible for epileptic seizures (Spencer and Spencer, 1994; Stringer and Lothman, 1992) via recurrent signalling of layer V pyramidal neurons (Dhillon and Jones, 2000). MTL epilepsy shares phenomenological characteristics with the psychedelic-induced states (e.g., spontaneous personal memory recollection). Most importantly, these experiences can be experimentally induced by increasing coupling between the PHC and the visual cortex (Barbeau et al., 2005).

A complementary brain mechanism can be formulated in light of the psychedelics’ effects on brain networks that control PHC activity. The PHC possesses high baseline connectivity with high-level cortical regions that make-up the so-called default-mode network (DMN) (Raichle and Snyder 2007; Ward et al., 2014). Under normal conditions, top-down inhibitory control over PHC activity is provided by projections from the precuneus, the posterior cingulate cortex (PCC), the retrosplenial cortex (RSC) and the medial prefrontal cortex (mPFC), that terminate on inhibitory interneurons within the PHC (Mohedano-Moriano et al., 2007; Morris et al., 1999; Vann, Aggleton, and Maguire 2009). Human PET studies have shown that the RSC, PCC and mPFC express notably high levels of serotonin 2A receptors (Erritzoe et al., 2009), and psychedelics are found to have a dysregulating effect on activity within these regions as shown with fMRI (Carhart-Harris et al., 2012; Tagliazucchi et al., 2014, 2016; Carhart-Harris et al., 2016; Palhano-Fontes et al., 2015), MEG and (Carhart-Harris et al., 2016; Muthukumaraswamy et al., 2013) and EEG (Riba et al., 2002; Kometer et al., 2015). This dysregulation effect likely compromises the ability of these regions to maintain top-down control over the PHC, and subsequently, may increase responsiveness of the PHC to stimuli that normally engage it, such as music (Mitterschiffthaler et al., 2007; Koelsch 2014; Trost et al., 2012). In support of this view is the finding that reductions in functional connectivity between the PHC and the RSC are observed after both psilocybin and LSD (Carhart-Harris et al., 2014; Carhart-harris et al 2016).

This naturally leads to the question *how* this could explain the vivid mental images people experience under LSD and music. What is it that the PHC-to-VC pathway does to produce such subjective experiences when modulated by the LSDxMusic interaction? Information flow from the PHC to the VC has been associated with to the encoding of learned representations, or top-down (prior) "predictions", for complex mental scenes (Aguirre and D'Esposito, 1999; Libby et al., 2012; Summerfield et al., 2006). The experience of perceiving complex scenes in the absence of visual input may therefore be the result of an enhanced gain on circuits that normally confer complex, top-down information about (a potential) visual scene. The present experiment showed that the modulation of PHC-to-VC effective connectivity by the combination of LSD and music, was associated with an enhancement in eyes-closed visual imagery. This association was however only present for the item assessing complex visual imagery item (i.e. concrete visual features, such as objects, entities and scenes), and not for the item that assessed simple visual imagery (i.e. low-level visual features such as colours and patterns). This lends indirect support for the view that LSD and music facilitate complex mental imagery via an abnormal engagement of backward projecting pyramidal neurons in the PHC that encode learned representations or "predictions" of complex visual imagery.

5.4.2 Implications for psychedelic therapy

Music alone is an effective medium for stimulating the imagination, and these effects of music are typically exploited in the context of conventional forms of music therapy (Castillo-Pérez et al., 2010; Erkkilä et al., 2011). The present experiment supports the hypothesis that under psychedelics, music-induced imagery is intensified. This suggests that psychedelics can be utilised to allow an enhanced engagement with mental images music on subjective experience. The findings of the present study help to elucidate the mechanisms by which music and psychedelics can do this in healthy volunteers. Further research is required to test the therapeutic value of enhanced mental imagery in the context of psychedelic therapy.

5.4.3 Study limitations and future directions

This experiment represented several limitations. First, no significant interaction effect was found between LSD and music on in-scanner subjective ratings for visual imagery, whereas connectivity analyses did show a significant interaction effect on PHC-VC coupling. Since enhanced PHC-VC coupling via the interaction between LSD and music correlated with complex visual imagery, this may be explained by small sample size and variance between individuals in their subjective responses to LSD and music. In addition, appraisal of the music may have played a role too: some participants may have disliked the genre of music or may not have been engaged with it for other reasons, such as being distracted by the considerable noise emitted by the MRI machinery.

Only one style of music was used in this experiment, and therefore the results may not be generalised to the experience of other music's. For example, the music used in this study did not contain clear rhythmicity, whereas some studies indicate effects of repetitive drumming on mental imagery (Hove et al., 2016). A study could be designed that incorporates more than one genre of music (E.g. emotionally relaxing music versus emotionally intensifying or arousing music).

Finally, the study group represented psychedelic-experienced users with no history of mental health issues. The present results can therefore not be extrapolated to a patient population, in which the combination of music and psychedelics is thought to be especially important for psychedelic therapy (Bonny and Pahnke, 1972). Subsequent work is needed to further our understanding of how music and psychedelics interact and how this may be useful for psychedelic-assisted therapy.

5.4.4 Conclusions

The present study revealed a positive interaction between LSD and music on PHC functional and PHC-VC effective connectivity. More specifically, a modulation of PHC to VC effective connectivity was observed that correlated positively with eyes-closed visual imagery, and particularly imagery of a complex and autobiographical nature. These results extend our understanding of circuitry involved in mental visual imagery and suggest candidate brain mechanisms for how LSD and music can work in concert to facilitate mental imagery. The study supports the view that psychedelics influence the experience of music, however, a large amount of work is required to further our understanding of psychedelic therapy and the roles of music.

“The listener does not find a simple reflection of his or her own expectancies. The music forms the listener’s experience, and in its unique negotiation of the tension between striving and grief, it creates knowledge of something that has been formerly unknown, something that asks to be integrated in the mind of the hearer”

Naomi Cumming

6 *Study 4* | Music-experience in psychedelic therapy

6.1 Background

The capacity of psychedelics to facilitate intense emotionality and autobiographical salient experiences was a primary motivation for their therapeutic use in the 1950s and 1960s (Busch and Johnson, 1950). Music was soon introduced within the therapeutic framework as a way to non-verbally guide patient's experiences into therapeutically meaningful directions (Hoffer, 1965; Bonny and Pahnke, 1972; Grof, 1980). Although modern psychedelic therapy sessions typically involve a 'hands-off' approach on behalf of the therapists, music is still widely used, and considered to be a valuable therapeutic tool. During the drug sessions, patients are typically encouraged to focus their attention inwards, while lying down in a relaxing position and listening to music. It is believed that in this way, music can facilitate experiences that have most therapeutic value, such as psychedelic peak experiences or autobiographical experiences.

The views behind this procedure were described in detail in the introduction chapter (chapter 1), and in subsequent chapters, data was presented that demonstrated that music-evoked emotion and music-evoked mental imagery are significantly modulated by LSD (chapters 3, 4 and 5). Although these studies support the hypothesis that the subjective response to music is intensified under psychedelics, these studies were performed in a population of healthy volunteers, and only used a short duration of music-listening and limited music styles. At present, there is no empirical data available on the experience of music under therapeutic conditions, and on the therapeutic functions that music may serve in this context.

This present study aimed to address this matter, by investigating the different ways music influences the subjective experience of patients undergoing psychedelic therapy with psilocybin for depression. This study used psilocybin, and not LSD, given most clinical evidence for safety and efficacy is for psilocybin, and psilocybin has a favourable half-life compared to LSD (which last longer). In addition, the study aimed to assess how the music-experience relates to the different aspects of the psilocybin-experience and to therapy outcomes. Nineteen patients with moderate to severe depression received psilocybin in a controlled therapeutic environment, and listened to a six-hour music playlist designed for this study. Clinical measures for depression were taken before and after the intervention, and patient's psilocybin-experiences were assessed via the 11-factor Altered States of Consciousness (ASC) questionnaire. Music-experiences were assessed by a semi-structured interview and Interpretative phenomenological analysis (IPA). Ratings of the interview-transcripts by researchers were subsequently correlated with measures for psilocybin-experience and reductions in depression.

Because music-evoked emotion (study 1 and 2) and music-induced mental imagery (study 3) are significantly modulated under psychedelics, and because both music (Gabrielsson and Wik, 2003) and psychedelics (Griffiths et al., 2006) can facilitate peak experiences, the influence of music on patient's experiences and on therapy outcomes was predicted to be substantial. These findings will be discussed in light of previous work, including a discussion on possible therapeutic mechanisms of music in psychedelic therapy, and on how the findings inform strategies for the use of music in psychedelic therapy sessions.

6.2 Methods

6.2.1 Approvals

The National Research Ethics Service London (West London) provided a favourable opinion for this study. The study was sponsored and approved by Imperial College London's Joint Research and Compliance Office (JRCO), and the National Institute for Health Research Clinical Research Network adopted the study. The National Institute for Health

Research/Wellcome Trust Imperial Clinical Research Facility provided approval for the study-site. A Home Office Licence for storing and dispensing Schedule One drugs was obtained.

6.2.2 Participants

Inclusion criteria for the study were moderate to severe major depression, as determined by the 21-item Hamilton Depression Rating scale (HAM-D), with absence of improvements despite at least two different pharmaceutical antidepressant treatments for a minimum of 6 weeks within the current depressive episode. Exclusion criteria included current or previously diagnosed psychotic disorder, diagnoses of psychotic disorders in immediate family members, a medically significant condition rendering the patient unsuitability for the study, history of suicide attempts that required hospitalisation, history of mania, having a blood or needle phobia, pregnancy, and current drug or alcohol dependence.

6.2.3 Experiment overview and procedures

Psilocybin was synthesised and obtained from THC-Pharm (Frankfurt, Germany), and formulated into 5mg capsules of psilocybin, by Guy's and St Thomas' Hospital's Pharmacy Manufacturing Unit (London, UK). Screening consisted of evaluating the patient's current and past physical and mental health. Patient-rated scales for the severity of depressive symptoms were completed during the screening visit and served as baseline measures. These included the 16-item Quick Inventory of Depressive Symptoms (QIDS) and Beck Depression Inventory (BDI). Written informed consent was given, and by the end of the screening, eligible patients met with the two therapists that would support them through the remainder of the trials.

A subsequent visit functioned as preparation for the session. This included conversations with the therapists about the patient's personal history, expectations for the sessions and education about the effects of psilocybin. The patient also had an opportunity to listen to samples of session music while wearing eye-shades, as a simulation-experience in preparation for their first session. The preparation visit lasted approximately 4 hours in total.

Following the preparation session, patients received two different dosages of psilocybin on two separate subsequent occasions, each separated by one week. In the first session, all patients received an oral dose of 10 mg psilocybin. This lower dose was intended to function like a “taster”, a preparation for the higher dose administered one week later. In the second session, all patients received 25 mg. Each session included only one patient and two therapists, and took place in a specially designed therapeutic environment. Each session started with arrival at the research facility at 9am, and with psilocybin being administered at 10.30am. The majority of patients were ready to leave the facility approximately 7 hours after administration. Transport from the research facility to home was organised ahead of the sessions and consisted of being accompanied by a close friend or relative. Patients also had the option of staying overnight in accommodation adjacent to the research facility, the night before and the night after the session.

Clinical improvement was defined as reductions in depression severity, and measured via the QIDS, completed by all patients at baseline, and 1 week and 6 months after the final psilocybin session. The different aspects of the subjective experience of psilocybin were measured with the 11-dimensional Altered States of Consciousness Scale (11D-ASC) (Dittrich, 1998) at the end the session. The structured interview assessing the patient’s experience of the music was always conducted 1 week after the high dose (25 mg) session. For a report on the clinical outcomes, see Carhart-Harris et al (2016) (Carhart-Harris et al., 2016).

6.2.4 Therapeutic setting

Considering the importance of the therapy setting (Johnson et al., 2008), all sessions took place in a specially designed therapy room within the Clinical Research Facility at Imperial College London. All unnecessary medical equipment was either removed or hidden, light quality was adjusted using Philips hue lamps. Drapes, cushions, plants, art paintings and artefacts were introduced to engender a cosy and comfortable climate.

After receiving psilocybin, patients were encouraged to relax in a reclined position on the bed and wear eye-shades. Two therapists were present on either side of the bed, and checked-in with the patient every 30-60 minutes, to obtain insight into how the patient’s subjective experience was unfolding, and to determine whether psychological support might be needed. Calming ambient music was played on entrance, but the session playlist (see appendix, chapter 8.3) was started upon ingestion of psilocybin. Patients had the option to listen to the music via high quality in-ear headphones (Sennheiser IE 800) or via a high fidelity standing stereo-speaker (Meridian DSP3200). Both headphones and speakers received the same audio signal, which allowed the music be played in synchrony and continuously through both channels. This set-up was considered helpful for:

1) providing a sense of continuation of the experience in case the headphones were pulled off or muted while the music was still playing.

2) helping the therapists have insight into the patient's experience, as well as how the patient responds to particular parts of the music.

3) allowing the music to be perceived not only via the ears, but also bodily and more spatially.

6.2.5 Music selection

The central purpose of the use of music in the present therapeutic study was consistent with that of early psychedelic-therapy studies, i.e. to facilitate personally meaningful experiences. In order to achieve this, researchers often emphasised the importance of adapting the music to individual patient's changing therapeutic needs, as their therapeutic experience unfolds dynamically (Hoffer 1965; Bonny and Pahnke 1972; Grof, 1980). For the present study, however, a standardized playlist was used to control for music as a potential confounding variable. Therefore, all patients were intended to listen to the same music playlist. In (rare) cases where the music selection was strongly disliked by the patient in the first session, or a strong preference was expressed to only listen to classical music, the music playlist used by John Hopkins was used (Richards 2015), which includes music originally suggested by Bonny and Pahnke (Bonny and Pahnke 1972).

Several of the musical works originally included in playlists for psychedelic-therapy (Richards 2015; Bonny and Pahnke 1972) are very familiar today. Examples include: "Samuel Barber - Adagio for strings" and "Beethoven – Piano Concerto 5". Such high familiarity may reduce the opportunity for patients to have a new experience with the music, unfettered by prior associations. In addition, a strong emphasis on music with "Christian religious" content may not be appropriate for individuals that are either non-religious or practice a different religion.

Therefore, a music playlist was designed for the present study, containing predominantly contemporary music such as the ambient-, neo-classical-, modern classical-, jazz- and diverse ethnic- music styles. The intention with this music selection was to transcend religious boundaries, and to support spiritual peak experiences within a secular framework. In addition, a part of the music-selection was tailored to the condition treated (i.e. depression), via a selection of music that reflected sentiments of sadness and grief, yet simultaneously, in the song's dynamical *narrative*, reflected themes of hope, change, beauty and personal empowerment. Music with such emotional sentiments was only played during peak drug intensity, on the assumption that this music would then reflect autobiographical and therapeutically significant content, and thereby increase the person's therapeutic engagement in the experience.

6.2.6 Playlist design

The design of the music-playlist was informed by Bonny and Pahnke (1972) (Bonny and Pahnke 1972) and the LSD psychotherapist and author Stanislav Grof (Grof, 1980), who defined different phases in psychedelic therapy sessions, where each phase is associated with a distinguishable set of psychological needs the music can serve. These phases are, in chronological order: "pre-onset", "onset", "building towards peak", "peak", "re-entry" and "return". In the present study, the durations of the phases were adjusted to the shorter duration of psilocybin's effects, compared with LSD. Furthermore, "onset" and "building towards peak", were grouped together as "ascent", and "re-entry" was named "descent".

6.2.7 The structured interview

The structured interview was always conducted one week after the final session, by the same researcher, apart from on one occasion. The interview consisted of four open questions: **1)** "Did the music influence your experience? And if so: in what ways?", **2)** "Can you comment on how the different styles of music influenced your experience? And which music did you prefer?", **3)** "Were there any aspects in the music that in particular influenced your experience positively?", and **4)** "Were there any aspects in the music that in particular influenced your experience negatively?". Additional questions were sometimes asked to clarify patient's responses if the interviewer felt the need to do so.

6.2.8 Theoretical approach of interview data-analysis

Interpretative phenomenological analysis (IPA) was chosen to analyse the interviews (Smith et al., 1997). IPA is an approach increasingly used in healthcare research (Biggerstaff and Thompson, 2008; Smith, 2011) that examines the meanings particular experiences hold to people. It is particularly appropriate for ascertaining the complexity (i.e. the quality and phenomenology of experience) behind patients' subjective experience of music during the therapeutic sessions, and has previously been used to investigate the benefits of music therapy interventions in cancer care settings (Pothoulaki et al., 2012)

6.2.9 Interview data analysis: Coding

Interviews were transcribed verbatim and checked for accuracy. All coding was done by at least two researchers, to increase inter-rater reliability. A step-by-step analysis of the data was followed (Smith, 2011). All transcripts were read through twice before carrying out the analysis. During the third reading, any phrases considered as especially pertinent in terms of how the music influenced the patient's subjective experience, were highlighted and coded into initial interpretations. At this stage, some text was assigned to more than one code when more than one interpretation could be made, and queries about the meaning of what was being said were recorded in a separate column. This process was repeated for four further transcripts.

Key words, phrases and initial interpretations from the first four completed transcripts were then comprehensively explored, leading to the creation of themes in a separate column. These themes were then used as guidelines for subsequent transcripts. As new themes emerged from these subsequent transcripts, all data were iteratively scrutinised and the list of themes refined. Throughout the process of analysis, codes were examined and discussed among the authors to decide which themes were the most accurate reflections of participants' experiences.

Following further discussion between authors, a final master list of themes emerged. The final stage of analysis involved the organisation of the list of themes into a more concise list of overarching, superordinate "clusters" or domains representing the patient experience of music, each of which contained a number of subsidiary themes.

After all transcripts were coded into themes and clusters, the presence of each unique theme and cluster across all patients' responses was calculated. This lead to a percentage index describing the frequency to which the themes and clusters were present within the total study population.

6.2.11 Ratings for music-experience

Three predictors for therapy-response were hypothesized: 1) "liking", referring to the degree to which the music styles and the music quality were liked, 2) "resonance", referring to the degree to which the music matched with or was "harmonious" with the intrinsic emotional state of the patient, and 3) "openness", referring to the degree in which the patient was open to, or accepting of the music-evoked experience.

Four researchers that were blinded to patient identifiers and treatment outcomes rated these variables for all 19 patients based on their interview transcripts. Ratings were done via a visual analogue scale, with five anchors presented. For the "liking", the question was formulated as "To what extent did the patient like or dislike the music?", with the following anchors on the response scale: "0 = strong disliking", "25 = major disliking, some liking", "50 = mixed disliking and liking", "75 = major liking, some disliking", "100 = major liking". For "resonance", the question was formulated as "To what extent was the music in resonance with the patient's subjective experience?", with the following anchors on the response scale: "0 = strong dissonance", "25 = major dissonance, some resonance", "50 = mixed resonance and dissonance", "75 = major resonance, some dissonance", and "100 = strong resonance". And finally, for the third, the question was formulated as "To what extent was the patient accepting of or open to the music-evoked experience?", with the following anchors on the response scale: "0= strong resistance", "25 = major resistance, some openness", "50 = mixed resistance and openness", "75 = major openness, some resistance" and "100 = strong openness".

6.2.12 Correlating music-experience with psilocybin-experience and therapy outcomes

Pearson correlation tests were performed between the three music-experience variables and ratings from the 11D-ASC. To reduce the number of comparisons, a principle component analysis (PCA) was performed on the 11 factors of the 11D-ASC. Varimax rotation was performed on the first 5 principal components (PCs) that explained over 95% of the variance (see Figure 6.3 for rotated PCs and their respective loadings). Subsequently, the three music-experience variables (liking, resonance and openness) were correlated with these 5 PC's. To test whether music-experience and drug-intensity are associated with different aspects of subjective experience of psilocybin, drug-intensity ratings were also correlated with all 5 PC's. False discovery rate (FDR) control was used to correct for multiple comparisons (Benjamini and Hochberg, 1995).

The average of the scores from all researchers was calculated for each patient, and a Pearson correlation test was applied to test for a relationship between these variables and 1) reductions in depressive symptoms 1 week and 6 months after the last session with 25mg psilocybin. Reductions in depressive symptoms were defined as the percentage reduction in scoring on QIDS relative to baseline (i.e. (score/baseline) x 100). To test for the discriminative value of music-experience variables in predicting therapy response, compared with mere drug-intensity, ratings for drug intensity were also correlated with reductions in depression.

6.2.13 Inter-rating reliability and discriminative validity of music-experience variables

Inter-rating reliability of researcher's ratings was tested by correlating ratings of all researchers with each other. To test for differences between music-experience and drug-intensity effects, ratings for drug-intensity were correlated with each music-experience value. The three music-experience variables were correlated with each-other to test for their discriminative value.

6.3 Results

A total of twenty participants were enrolled in the trial, including 14 males and 6 females, with an average age of 44.1 ±11 years. Ethicities included 15 white, 3 black, 1 asian, and 1 hispanic. 11 were unemployed. Average years of depression was 17.7 ±8.5, and average severity of depressive symptoms was 19 ±2.7 on QIDS-16, 35 ±7.4, 23.9 ±5.4. The average number of different medications used in the past was 4.6 ±2.6, and 17 out of 20 underwent psychotherapy in the past. 18 had higher education. Weekly alcohol use in units was 3.7 ±6.5, and previous (life-time) use of psilocybin was 0.7 ±1.1. For more details on demographics see Carhart-Harris et al (2016, 2017).

Analayses of the interview resulted in the identification of four separate groups, that include clusters of related themes. These groups were: 1) “Welcomed influences”, including all influences of music on subjective experience that were described as welcomed, wanted, accepted or appreciated (Figure 6.1)), were identified in 18 out of 19 patients (95% of total); 2) “Unwelcomed influences”, including all experienced influences of music that were described as unwelcomed, unwanted, unacceptable or unappreciated (Figure 6.1)), were identified in 10 out of 19 patients (53% of total); 3) “Appreciated music styles and playlist features”, including all aspects related to music genres, styles, and playlist design, that were appreciated or liked, (Figure 6.2), and were identified in all 19 patients (100% of total) ; 4) “Unappreciated music styles and playlist design”, including all aspects of music genres, styles and playlist design that were not appreciated or were disliked (Figure 6.2), were identified in 11 out of 19 patients (58% of total). Here, the term “music styles” refers broadly to the instrumentation, compositional-, genre- and acoustic- features of the music. The term “playlist design” refers to all aspects related to the selection and structuring of the music into the full music playlist.

The figures displaying the four groups (Figures 6.1 and 6.2) include the clusters present in more than 30% of the respective group, and the themes present in more than 30% of the respective cluster. All patient’s quotes of themes present in each of these groups and clusters, are displayed in separate tables (Table 1-11). It is important to emphasise that the identification of a theme in a patient’s experience, and subsequently the including of that theme in counting its presence in the total population, does not allow us to make any statements on the duration that this theme was present in the patient’s total experience. E.g. one patient may have experienced a sense of irritation in response to one particular song, and therefore the theme “irritation” under the cluster “intensification” in the group “unwelcomed influences” is present. But this does not imply that the patient experienced persistent feeling of irritation during his or her experience. In addition, the measure also only allows the capturing of spontaneous mentioning and elaborations on the subjective experience of the music, as opposed to the questions targeting (and biasing) specific facets of the patient’s experience.

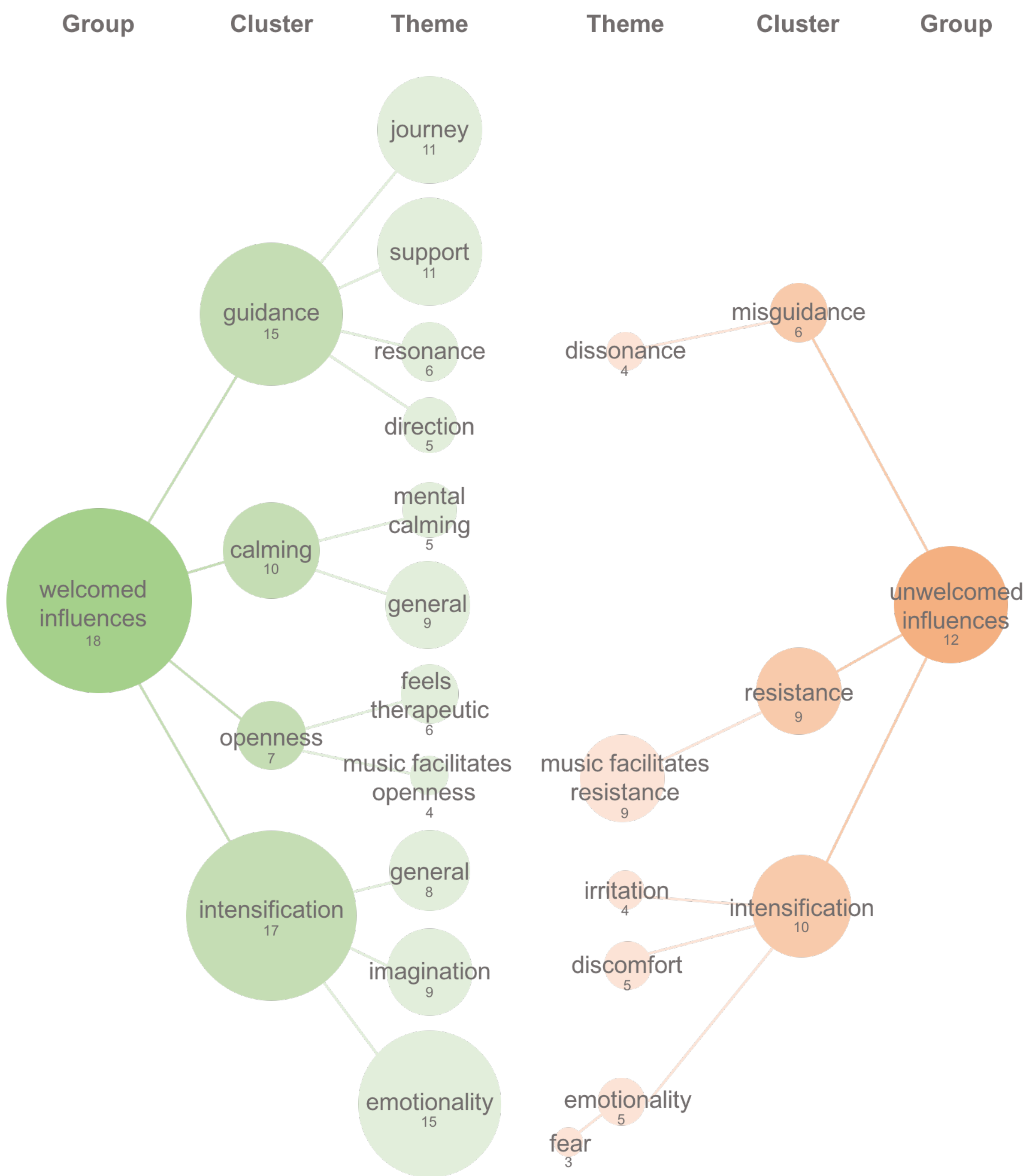

Figure 6.1 | Welcomed and unwelcomed influences of the music. Welcomed influences are displayed on the left in green, and unwelcomed influences are displayed on the right in red. All clusters and themes that are defined as an accepted or welcomed influence of the music on subjective experience. The figure displays cluster present in more than 30% of all participants, and per cluster the themes that were present in more than 30% of the cluster. The numbers below the group-, cluster- or theme-name, refers to the total number of patients that referred to this. The size of the circle is proportional to the percentage of patients referring to the group, cluster or theme.

6.3.1 Welcomed influences: Intensification

The most prominent cluster in the group "welcomed influences", including 17 out of 19 patients (88% of total), refers to themes that describe an "intensification" of the subjective experience by the music. Within this cluster, themes that describe an "intensification of emotion" were identified in 15 out of 17 (82% of cluster), including descriptions of music enhancing or changing emotions. Importantly, the emotion-evoking effects that were welcomed, showed diverse emotional valence, and included descriptions of the music facilitating "happiness" or strong "ecstatic" experiences, as well experiences of the music intensifying "tearfulness".

Themes describing an "intensification of imagination" were identified in 9 out of 17 (53% of cluster). This included statements of the music evoking vivid and complex mental imagery, and of the concrete imagery related to specific aspects of the music. Such as for example the ethnic "Indian" style of the music being associated with "seeing an Indian temple". 8 out of 17 patients (47% of cluster), mentioned a "general intensification" effect of the music, without specifically referring to this being an intensification of emotionality, imagery or others. Other themes, present below 30% in the cluster "intensification", include effects of music on "personal thoughts or memories" (2/17, 12% of cluster), music facilitating a "sense of transcendence" (2/17, 12% of cluster) and music enhancing "ego-dissolution" (2/17, 12% of cluster) (Figure 6.1). See Table 6.1 for a listing of all themes present in the cluster "intensification".

Table 6.1 | Welcomed influences: Intensification. A list of all the themes and respective quotes by patients, that were present in the cluster "intensification"

#	Quote	Theme
1	"The level of intensity of the music made things in my mind seem more intense."	General intensification
3	"[The music] can amplify the emotions, either negatively or positively."	Emotionality
	"Make you feel happy when there's a good song on."	Emotionality (happiness)
	"it was all good […] all in the same area where it can get people meditating, or releasing, or just chilling out to it."	Emotionality
	"Your emotion goes with that [music] and the happy feeling, and its like all	Emotionality

	connected.”	(happiness)
4	“[The music] made me even more emotional.”	Emotionality
	“The sad songs would bring painful memories on, more happy songs would make me think of a really good period in my life.”	Personal thoughts or memories
	“I didn’t like the emotional music the first experience cause I didn’t want to cry, but actually, you know, the second time I sort of enjoyed crying to this music.”	Emotionality (tearfulness)
	“[The soothing music] brought up nice images, like I imagined I was an unborn child and I felt very safe. Every new song could bring a different image, and I couldn’t finish the previous one that I was thinking about. It was interesting.”	Imagination
5	“[The music] made me see what I considered ephemeral things, like a sense of a mother and a sense of a child. And their behaviour was definitely informed by the music.”	Imagination
	“[The music] caused different feelings.”	Emotionality
	“[The music] caused the different imagery.”	Imagination
6(2)	"There were moments when I felt just this burst of joy."	Emotionality (happiness)
	"And I connected [the music] very strongly thinking about Rembrandt who I love."	Personal thoughts or memories
	"So I just felt overwhelmed with joy and gratitude to have that [music] in my life."	Emotionality (gratitude)
	"There was one piece that I knew very well and it reminded me of somebody."	Personal thoughts or memories
7	“Some bits of it were otherworldly.”	Imagination
	“I could almost picture myself there.”	Imagination
	“[The music] seemed to heighten the experience.”	General intensification
	“[The music] stirred something.”	Emotionality
	“[The music] seemed to fit the space that I was inhabiting. I felt a dissolution, where you sort of dissolve. And I felt the music after the quiet ambient music, in the beginning, emphasized that beautifully. And it definitely enhanced it.”	General intensification, Ego-dissolution
9	“There's one track [Greg Haines - Azure] that gets really really really intense.”	General intensification
	“[Greg Haines - Azure] I felt like I was sort of the highest I could get, it was like the absolute, the top of everything.”	Sense of transcendence
	“[Greg Haines - Azure] really really beautiful, overwhelming, but really peaceful as well.”	Emotionality
10	“[The music] helped me to emotionally connect.”	Emotionality
	“I wouldn’t say that I felt sad, but, I obviously cried, but I don’t know why I did	Emotionality

	(half-laugh)- but I wasn't sad."	(tearfulness)
	"if I'd listened to anything else then I probably would have had a different experience [emotionally]."	Emotionality
	"At the beginning, as the effects starts to, you know, creep up on me, it was quite "Chinese-ey"? And (giggles) the bit where I saw the psychedelic Chinese dragon."	Imagination
	"I was tearful at some points."	Emotionality (tearfulness)
11	"In terms of movement, of the patterns going along with the music."	Imagination
	"Indian music, where I was seeing an Indian temple."	Imagination
	"Setting the place, an Inca princesses singing and seeing the terraced Inca-type setting."	Imagination
	"The music was influencing the movements and influencing the setting."	Imagination
	"During that same Indian piece, that's when I was dancing for Shiva and then I was Shiva."	Imagination
	"[The music] influenced this sensory perception."	Imagination
	"Saying that it made me sad or it made me happy, those words are actually not irrelevant, a little too mild almost to explain what it was."	Emotionality
	"I felt ecstasy, "ek-stasis". It was hard to separate out what's happening here, from what's happening here, from what's happening here."	Emotionality (ecstasy)
12	"[The music] helped with the visual stuff and the mood."	Imagination, Emotionality
	"the visuals … [The music] kind of opens up your imagination in a way, your imagination is much easier to picture. One of the songs created imagery of a "wooden bannister" that had a shape, it had a texture and a material, with some water and marbles with rainbows in it. I could picture it really clearly."	Imagination
	"[the music and the experience] was a symbiotic kind of thing."	General intensification
	"That piece of music was probably the peak of positivity, it was almost like a subdued kind of ecstasy, you know, it was so amazing. It was such a beautiful feeling."	Emotionality (ecstasy)
	"[Experiencing a challenging influence of the music] wasn't a bad thing you know, it opened you up."	Openness
	"The music is kind of changing your state of mind almost, or putting you on a different resonance."	General intensification
13	"It feels like your mood, or the the intensity of the drug, it feels like it goes with the music."	Emotionality, General intensification
14	"Under the influence of psilocybin,[the music] absolutely takes over."	General

		intensification
	“Normally when I hear a piece of sad music, or happy music, I respond through choice, but under psilocybin I felt almost that I had no choice but to go with the music.”	Emotionality, Ego-dissolution
	“And I did feel like [the music] opened up to grief, and I just was very happy for that to happen.”	Emotionality (tearfulness)
	“Primitive music felt like it was taking me under, I had no choice.”	Ego-dissolution
	“The patterns of the sound were doing something to me visually, and I responded emotionally to the visuals, and the visuals were directly related to the sound.”	Emotionality, Imagination
15	“It’s so beautiful it just made me cry.”	Emotionality (tearfulness)
16	“It changed the sort of imagery in my head, it didn’t make it any better or worse, but it had a definite impact”	Imagination
	“It felt like everything added towards the experience rather than took away”	General intensification
17	“The music evoked a lot of emotions.”	Emotionality
	“I had a sort of ecstatic experience.”	Emotionality (ecstasy)
	“That seemed to be the point at which I was kind of carried away, in this ecstatic rapture.”	Emotionality (ecstasy)
	“Clearly the music enhanced the emotional experience.”	Emotionality
	“I suppose church-type music, I think was responsible for enhancing the religious experience.”	Emotionality (spirituality)
18	“My experience seemed sometimes to coincide with the lightness of the music into the light place and the darkness of the music to the dark.”	Emotionality
	“There was a specific moment when I felt as though I was being given birth to the universe, and I semi-recall there was this sort of crescendo of music at that point, that was a very strong point in the journey for me.”	Imagination, Sense of transcendence
	“When I was born into the universe, you know, everything dropped away apart from these slight tethers that were holding me back, and I was into the vastness of the universe, and that could have been when the music stopped, because I remember at that particular point looking at this immense void in front of me.”	Sense of transcendence
19	“The music did affect [the experience].”	General intensification
	“The music just made it more emotional.”	Emotionality
	“Yeah, it definitely served the function of helping emotions flow.”	Emotionality

6.3.2 Welcomed influences: Guidance

The second most prominent cluster of welcomed influences, includes themes that depict the music as a source of "guidance". This cluster was mentioned by 15 out of 19 patients (79% of total). Within this cluster, statements that the music provided a "sense of being on a journey" were identified in 11 out of 15 (73% of cluster). This included descriptions of the music being experienced as a "vehicle" that "transports" or "carries" the listener forward, providing a sensation of "traveling" to different psychological "places".

Themes describing the music as a source for psychological "support" were identified in 11 out of 15 (73% of cluster). This includes various statements of the music providing a sense of "grounding", "help" and "reassurance". Descriptions of the music being in tune with, or in "resonance" with the person's intrinsic emotional state were identified in 6 out of 15 (40% of cluster). Rather than describing the music as evoking emotion, this theme is defined by statements of the music being experienced as "fitting", "following" or "matching" present emotional states.

Finally, 5 out of 15 of patients (33% of cluster) referred to the music as providing a "sense of continuity and direction", this included statements of music providing a sense of connection between different parts in the experience, making the experience feel "driven" by the music and "flowing" into a certain direction (Figure 6.1). See Table 6.2 for a listing of all themes present in the cluster "guidance".

Table 6.2 | Welcomed influences: Guidance. A list of all the themes and respective quotes by patients, that were present in the cluster "guidance".

#	Quote	Theme
1	"I think that it was comforting, knowing that the music was there, because it was there the whole period, the music was always in the background, so in in a way it grounded me."	Sense of support
	"Having the music in the background, it somehow just was helpful."	Sense of support
	"[The music] gave me a sense of safety during the experience."	Sense of support
	"[The music] was structured in line with the way the effects of the drug were."	Resonance
	"It was there throughout, I think it was just that continuity."	Sense of continuity

		and direction
2	“The music was spot on with my feeling.”	Resonance
	“[The music] was following my emotion at the time.”	Resonance
	“I could see that there was a great effort to put the music together in a way that it followed the experience as it was meant to be.”	Resonance
	“[The music helped with the] relaxation I went through.”	Sense of support
4	“When I had this difficult moment and [I was] encouraged to focus on the music and I put the headphones on, the song that came up was very soothing and it made me calm down and get out of that.”	Sense of support
	“[The soothing music] brought up nice images, like I imagined I was an unborn child and I felt very safe. Every new song could bring a different image, and I couldn’t finish the previous one that I was thinking about. It was interesting.”	Sense of support
6(2)	"It all just flowed."	Sense of continuity and direction, Sense of support
7	“It began quite ambient-like, quite relaxing, which I felt was good. It calmed you in the experience.”	Sense of support
	“[The music] made me feel that I was in different locations.”	Sense of being on a journey
	“I could almost picture myself there.”	Sense of being on a journey
	“I felt as if I was travelling.”	Sense of being on a journey
9	“And the music felt really open itself.”	Resonance
	“[Greg Haines - Azure] just builds and builds. You're holding on to an extent, you just kind of go up and you're like ‘ok, where am I? Can I go any further?’”	Sense of being on a journey
	“That saying, going in and through it, really helped me throughout the whole experience.”	Sense of support
10	“it was all kind of a journey.”	Sense of continuity and direction, Sense of being on a journey
	“It was seamless- apart from the breaks. But after breaks they would put the headphones in and I would go straight back into that world.”	Sense of continuity and direction
	“Without it I would have gone mad.”	Sense of support

11	“The most facilitative to the trip were the straight on classical pieces.”	Sense of support
12	“[The music] helped with the visual stuff and the mood.”	Sense of support
	It was like a rollercoaster, you move with the music.”	Sense of being on a journey
	“You were led up and then brought down and led up.”	Sense of being on a journey
	“The music is kind of changing your state of mind almost, or putting you on a different resonance.”	General intensification
13	“I think the way it was guiding me. It was good.”	Sense of support
	“It’s [the music] definitely necessary. It kind of cuts you off from where you are at that time.”	Sense of being on a journey
14	“I feel the music in large part drove a lot of the experience.”	Sense of continuity and direction
	“I did feel as if I was being held”	Sense of support
	“[The music] took my thinking and my experience to uncomfortable places, but I was kind of reassured in the experience.”	Sense of support
	“There was something there that meant that, you know, ‘I’m going to take you on a ride here, but I promise I won’t abandon you. It’s just going to be tough, and you know, you’re going through the grinder here, but you won’t be left in pieces.’ That seemed to be what the music was saying to me.”	Sense of support, sense of being on a journey
16	“The music took you to the places you needed to be.”	Sense of support, sense of being on a journey
	“It felt we had a profound relationship, between my heartbeat and the beat of the music.”	Resonance
	“It felt like the music picked you up and carried you to the next part, and the next piece, and it was the vehicle that moved you.”	Sense of being on a journey, Sense of continuity and direction
	“There was a point and I didn’t want music anymore, I didn’t want anything but I definitely think the music sort of transported there to where you should be”	Sense of being transported
	“It felt like it all fitted the experience”	Resonance
17	“That seemed to be the point at which I was kind of carried away, in this ecstatic rapture.”	Sense of being on a journey
	“I was able to just put the headphones on and the mask on, and really enjoy it.”	Sense of support

	"The music definitely assisted me."	Sense of support
18	"The music both took me to very beautiful places and to incredibly dark places."	Sense of being on a journey
	"My experience seemed sometimes to coincide with the lightness of the music into the light place and the darkness of the music to the dark."	Resonance
	"I went to a very dark place."	Sense of being on a journey
	"It was a woman's voice, it was a sort of operatic voice, and first it was beautiful because, you know, I was following it and it took me to a beautiful place."	Sense of being on a journey
19	"Yeah, it definitely served the function of helping emotions flow."	Sense of support

6.3.3 Welcomed influences: Calming

10 out of 19 patients (53% of total) described calming effects of the music. From this cluster, 9 out 10 (90% of cluster) described "general calming" effects, whereas 5 out of 10 patients (50% of cluster) described the music as providing "mental calming" effects, including sensations of peacefulness and of the music calming and "slowing the mind". 1 out of 10 (10% of cluster) described the music to help feel more physically relaxed. Calming effects of music often referred to ambient music by Brian Eno, Harold Budd and Stars of the lid. See table 2 for a listing of all themes present in more than 30% of the cluster "guidance" (Figure 6.1). See Table 6.3 for a listing of all themes present in the cluster "calming".

Table 6.3 | Welcomed influences: calming. A list of all the themes and respective quotes by patients, that were present in the cluster "calming".

#	Quote	Theme
1	"The music helped me to be relaxed."	General calming
	"My body, my breathing, was better when the medicine was wearing off, because the music was very mellow."	Physical calming
2	"There was a part of the experience where I felt really relaxed. It was a very relaxed music and I was feeling very relaxed, so definitely there was an influence there."	General calming
	"[The music helped with the] relaxation I went through."	General calming

3	"it was all good […] all in the same area where it can get people meditating, or releasing, or just chilling out to it."	General calming, Mental calming
4	"When I had this difficult moment and [I was] encouraged to focus on the music and I put the headphones on, the song that came up was very soothing and it made me calm down and get out of that."	General calming, Mental calming
6(1)	"It was relief, because I hadn't liked the ones before."	General calming
	"Just relief really when I just felt oh, its ok, its ok."	General calming
7	"It began quite ambient-like, quite relaxing, which I felt was good. It calmed you in the experience."	General calming
	"It did help to calm and slow the mind."	Mental calming
9	"[Greg Haines - Azure] *really really* beautiful, overwhelming, but really peaceful as well."	Mental calming
10	"More often than not I was sort of peaceful."	Mental calming
	"I was really calm and peaceful and relaxed."	General calming, Mental calming
13	"And particularly once it starts to mellow out towards the end, you do feel that more relaxed."	General calming
15	"There was a piece that was quite calming, so that was very positive."	General calming

6.3.4 Welcomed influences: Openness to music-evoked experience

7 out of 19 patients (37% of total) made statements about their own attitude of openness towards the influences of the music, and in addition, about the effects of music on their attitude of openness. From this cluster, 6 out of 7 (86% of cluster), referred to the "importance" and the "purpose" of being open to "challenging experience" evoked by the music, and that this felt like an important part of the therapeutic process. This included statements of accepting being deeply emotionally moved by the music, and the music helping to "face" or "connect with" the listener's "unresolved" inner conflicts. 4 out of 7 (57% of cluster) described that some music specifically helped to enhance their attitude of openness, such as statements that "the music opened [him/her] up" or that because of the music was "well-chosen", the listener "felt open to it all" (Figure 6.1). See Table 6.4 for a listing of all themes present in the cluster "openness to music-evoked experience".

Table 6.4 | Welcomed influences: openness to music-evoked experience. A list of all the themes and respective quotes by patients, that were present in the cluster “intensification”.

#	Quote	Theme
3	“That’s not what it’s about, just skipping to the next track to the good stuff. It’s there, that you don’t like it, then deal with it (chuckles), so that’s our approach.”	Openness to challenging experience feels therapeutic
4	“I didn’t like the emotional music the first experience because I didn’t want to cry, but actually, you know, the second time I sort of enjoyed crying to this music.”	Openness to challenging experience feels therapeutic
	“In the first experience I was a bit annoyed that this music is too emotional, but I’m sort of thinking it was good for me, so I wouldn’t consider it as bad in the end.”	Openness to challenging experience feels therapeutic
6(2)	"It all flowed, I opened myself to it, and it was totally positive."	Music facilitates Openness
9	“As far as positivity goes it was amazing. Yeah, *really, really, really* helped to open me up... [The music] really opened things up.”	Music facilitates Openness
	“I can even view the negative moments as positive in a way because they served a purpose. The purpose was to sort of let me face the darkness, and my demons, I guess. It was beautiful at times, but also… yeah, the darker moments really helped to reflect on and connect with your demons, your unresolved shadows.”	Openness to challenging experience feels therapeutic
	“[Henry Gorecki – Symphony of sorrowful songs] was uncomfortable, but not bad. That was necessary I feel.”	Openness to challenging experience feels therapeutic
	“There's the odd chord change as well within other parts of the music, that affected me negatively, but that all served a purpose.”	Openness to challenging experience feels therapeutic
	“It wasn't like having Justin Bieber for 6 hours, ‘everything's jolly and light and bright and saccharine!’”	Openness to challenging experience feels therapeutic
	“It was such a well chosen playlist I felt that I was opened to all of it."	Music facilitates openness
12	“[Experiencing a challenging influence of the music] wasn’t a bad thing you	Openness to challenging

	know, it opened you up."	experience feels therapeutic
		Music facilitates Openness
14	"And I did feel like [the music] opened up to grief, and I just was very happy for that to happen."	Openness to challenging experience feels therapeutic
		Music facilitates Openness
	"It wasn't particularly pleasant in any way, but extraordinarily powerful."	Openness to challenging experience feels therapeutic
16	"There was a point and I didn't want music anymore, I didn't want anything, but I definitely think the music sort of transported there to where you should be"	Openness to challenging experience feels therapeutic

6.3.5 Unwelcomed influences: Intensification

The most prominent cluster, including 5 out of 10 patients (50% of cluster), described music to "intensify" emotions they did not want to feel, such as increased "fearfulness", "sadness" or "fear". In addition, 5 out of 10 (50% of cluster) said made statements about the music creating a sense of "discomfort", including "unpleasant" or "uncomfortable" experiences, and 4 out of 10 (40% of cluster) described "irritation" as a consequence of the music. In less than 30% of the cluster, the music was described as bringing mental imagery, thoughts or memories that were unwelcomed, a sense of puzzlement, inner conflict, and tension, or a "dark atmosphere". This cluster of unwelcomed "intensification" influences, forms a contrast with the cluster of themes describing intensification as a welcomed influence (Figure 6.1 and Table 6.1). See Table 6.5 for a listing of all themes present in the cluster unwelcomed "intensification".

Table 6.5 | Unwelcomed influences: intensification. A list of all the themes and respective quotes by patients, that were present in the cluster "intensification".

#	Quote	Theme
3	"It was crazy, it was like: change the song, please change the song! [Interviewer: Like a discomfort?], big time."	Discomfort
4	"Very trippy music, making me more scared when I had this difficult phase, that I was thinking 'ah, I'm going crazy!'"	Emotionality (fear)
	"In the first experience I was a bit annoyed that this music is too emotional"	Irritation
	"I didn't like the emotional music the first experience because I didn't want to cry."	Emotionality (tearfulness)
5	"My response to the music was one of fear, I guess, in part, because I viewed part of the music as this really sombre, serious, negative, cynical way of thinking, like it was my funeral, or like something really profound was about to happen, or death. And it was the music that was informing that feeling."	Emotionality (fear, sadness), Imagination, personal thoughts or memories
	"In the period where it wasn't so intense, when I cried a lot, the music elicited that sort of response."	Emotionality (tearfulness)
	"It accentuated any sense of like… emotional music, it just made me even sadder."	Emotionality (sadness)
6(1)	"A sense of irritation, frustration, and sense of lowering mood."	Irritation, Emotionality (sadness)
	"It's music that I can't listen to, I find it irritating or agitating."	Irritation
	"I felt quite torn."	Inner conflict
7	"Creating puzzlement rather than just accepting the music. […] 'Why is that person singing it in that particular way?' and I felt myself spending a lot of time thinking about that. Trying to work out why she was singing it in that particular style."	Puzzlement
9	"[Some of the music influenced the experience by] making things seem darker."	Dark atmosphere
	"Uncomfortable chord changes."	Discomfort
13	"With a higher tempo everything feels a bit more tense."	Tension
15	"I wanted to explore a certain experience or vision, but the music changed that. I was experiencing these geometric shapes which were seeming to construct themselves into something that I was beginning to understand, but then the music interrupted that and changed it and I was slightly annoyed by that."	Irritation

	“The piano pieces, irritated me. It was like little needles.”	Irritation, Discomfort
	“The piano playing was irritating, because I found it quite amateurish.”	Irritation
17	“There was some sort of Indian-style music, I think I found it a bit creepy at the time.”	Emotionality (fear)
19	“Made me a bit more emotional, more vulnerable.”	Emotionality
	“A bit annoying”	irritation
	“What I was experiencing at the time, it was you know, unpleasant”	Discomfort
	“Made me feel ‘uurgh’”	Irritation
	“Some of [the music] was uncomfortable.”	Discomfort

6.3.6 Unwelcomed influences: Resistance to music-evoked experience

9 out of 19 patients (47% of total) described feelings of “resistance to the music-evoked experience”. This includes statements of “not liking” or “not wanting” the subjective effects of the music. This cluster of unwelcomed influences contrasts the cluster of themes describing an “openness to music-evoked experience”, as a welcomed influence (see Table 6.4 and Figure 6.1). See Table 6.6 for a full list of all themes in the cluster “intensification”.

Table 6.6 | Unwelcomed influences: resistance to music-evoked experience. A list of all the themes and respective quotes by patients, that were present in the cluster “resistance to music-evoked experience”.

#	Quote	Theme
3	“It was crazy, it was like: change the song, please change the song! [Interviewer: Like a discomfort?], big time.”	Music facilitates resistance
4	“I didn’t like the emotional music the first experience because I didn’t want to cry.”	Music facilitates resistance
5	“I worried that I let [the music] shape this sort of melancholy.”	Music facilitates resistance
	“There was resistance, massively, to everything, every sort of sensory input I had a fearful response. I was afraid to open my eyes, I was afraid to do anything, I was afraid that this sort of music was the last thing I’d ever hear.”	Music facilitates resistance
	“But I listen to a lot of similar kind of music on my own, so obviously, it does move me, whether or not I admit that, it does shape my emotions and my	Music facilitates resistance

	moods.”	
6(1)	"I was trying to suppress [the anger]."	Music facilitates resistance
7	“Creating puzzlement rather than just accepting the music. [...] ‘Why is that person singing it in that particular way?’ and I felt myself spending a lot of time thinking about that. Trying to work out why she was singing it in that particular style.”	Music facilitates resistance
9	“There were times when I thought ‘I don't like the effect of this, on me.’”	Music facilitates resistance
14	“I noticed I didn’t wanna hang around for the last hour, that version of Joe Cocker, ‘Love Lift Us Up’.”	Music facilitates resistance
	“That is my issue sometimes, not being willing to go with the experience [of disliked music], but there’s a lesson in there for me.”	Music facilitates resistance
15	“It was very difficult to totally let go because I thought that, I felt that if I totally let go I might not be able to bring myself back.”	Music facilitates resistance
16	“There was a point, and I didn’t want music anymore, I didn’t want anything.”	Music facilitates resistance

6.3.7 Unwelcomed influences: Misguidance

6 out of 19 (32% of total) made statements about the music providing a sense of “misguidance”, this cluster primarily includes descriptions of the music being a “mismatch” or being incongruent with the unfolding subjective experience. This cluster, named “dissonance”, was present in 4 out of 6 (67% of cluster), and forms a contrast with the welcome influence “resonance”, when the music was experienced as harmonious, or a good match, with the subjective experience. Other themes of misguidance, present in less than 30%, include descriptions of the “music feeling intrusive”, the music being “unable to positively influence a challenging experience”, the music giving a “sense of being manipulated”, the music giving a “sense of unmet potential”, or the music giving a sense of “foreboding”, as if something “bad” was going to happen. This cluster of unwelcomed influence contrasts the cluster of themes describing a sense of “supportive” and “helpful” guidance, as a welcomed influence (see Table 6.2 and Figure 6.1). See Table 6.7 for a full list of all themes in the cluster “misguidance”.

Table 6.7 | Unwelcomed influences: misguidance. A list of all the themes and respective quotes by patients, that were present in the cluster "misguidance".

#	Quote	Theme
5	"My response to the music was one of fear, I guess, in part, because I viewed part of the music as this really sombre, serious, negative, cynical way of thinking, like it was my funeral, or like something really profound was about to happen, or death. And it was the music that was informing that feeling."	Sense of foreboding
	"Everything was like 'aaaaahh you're about to die!' (singing in dramatic voice)."	Sense of foreboding
6(1)	"To me [the music] didn't feel real."	Dissonance
	"I was sort of feeling bad, because I wanted to work with it."	Sense of unmet potential
	"I sensed the potential for a really profound experience, but I couldn't meet [that potential] with music that I felt was quite mediocre."	Sense of unmet potential
14	I've heard classical music perform live and wonderfully, but I'm kind of suspicious of it now. There's something malevolent in it, maybe not totally, but from its inspirations, because it was intended to be nationalistic and patriotic."	Sense of being manipulated
15	"I was very aware of the influence of the music, which I found at times intrusive."	Music feeling intrusive, Dissonance
	"The music was discordant"	Dissonance
	"I just found it [the piano music] grating. Intrusive even. Maybe the way it was being played."	Music feeling intrusive
18	"I went to a very dark place with that beautiful music still playing for a while, and then it got darker. The music didn't get dark and then I went to the dark place, I went to the dark place with the light mystical music."	Dissonance, Music unable to positively influence challenging experience
	"There was a kind of out-of-place piano, that was almost sort of 'hunky-tunky', but that just didn't sort of fit really."	Dissonance
	"I think the music lured me to this beautiful place, and then things started to become dark even with this beautiful music still playing."	Music unable to positively influence challenging experience
	"I can remember thinking 'this is beautiful music, why am I going to this dark place?' It didn't line up with what had gone on before, you know, that pattern. I just felt as if I was being manipulated, being duped almost."	Dissonance, Sense of being manipulated
	"A little conversely, the light music at one point took me to a place where I	Sense of being

	thought I was safe, and it became unsafe, and the music was playing a trick with me, you know, sort of giving me a false sense of security.”	manipulated
	I think really only that that luring beautiful woman’s voice that took me initially to a beautiful place, and then it took me to a really bad place. A *really* bad place.”	Transportation to “bad place”
	“That was profound, because it was as though there was somebody orchestrating that, somebody manipulating that, you know, not in a good way.”	Sense of being manipulated
19	“I couldn’t connect with the music.”	Dissonance

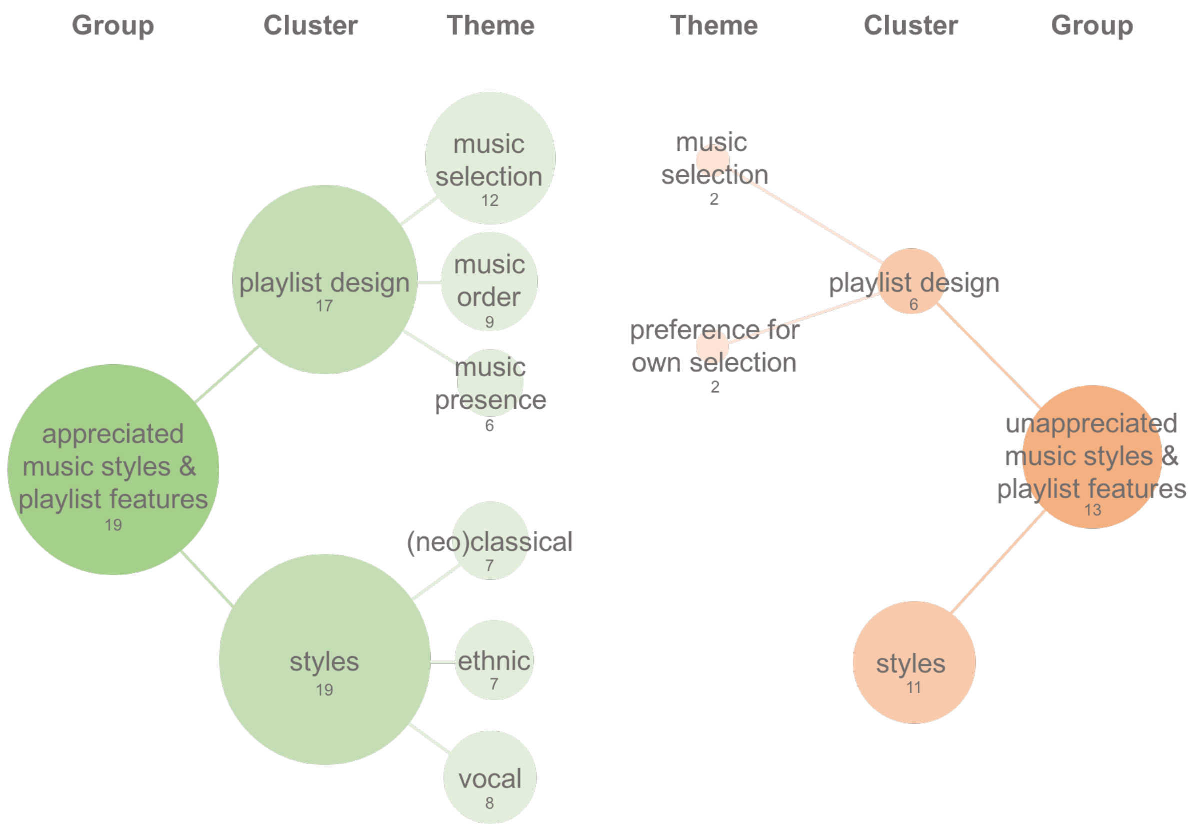

Figure 6.2 | Appreciated an unappreciated music styles and playlist features. Appreciated music styles and features are displayed on the left, in green, and un-appreciated influences are displayed on the right, in red. The figure only displays cluster present in more than 30% of all participants, and per cluster the themes that were present in more than 30% of the cluster. The numbers below the group-, cluster- or theme-name, refers to the total number of patients that referred to this. The size of the circle is proportional to the percentage of patients referring to the group, cluster or theme.

6.3.8 Appreciated music styles and playlist features: Music styles

All 19 patients referred to some music styles within the music playlist that they especially appreciated (Figure 6.2). Most frequent were positive statements about “ethnic or cultural music”, present in 8 out of 19 patients (42% of cluster), such as “Indian”, “Spanish” or “African” music styles (e.g. Jon Hassel, Ry Cooder & Ronu majumdar). Positive statements about music with human voice were mentioned by 7 out of 19 patients (37% of cluster). Importantly, this refers to vocal music either without lyrics or music with lyrics in a foreign language (e.g. *The Journey* by Ludivoco Enaudi, and Enya’s *sumiregusa*). One other music style that was frequently appreciated by 7 out of 19 (37% of cluster), was neo-classical music (e.g. Max Richter or Olafur Arnalds) or classical music (e.g. Henryk Gorecki or Arvo Part). Apart from these styles, the appreciated music styles showed a noticeable diversity. In less than 30%, positive statements were directed to “music with crescendo” (5 out of 19, 26% of total), “powerful music” (4 out of 19, 21% of total), and only 1 to 2 out of 19 made explicit statements about their appreciation for specific instruments, such as violin, guitar, piano, or “music with a solid drone”. See table 6.8 for a full listing of all themes referring to music styles that were explicitly appreciated.

Table 6.8 | Appreciated music styles and playlist features: music styles. A list of all the themes and respective quotes by patients, that were present in the cluster “music styles”.

#	Quote	Theme
1	“I liked the piano pieces.”	Piano music
	“A Spanish piece with a guitar and the singing, that was quite beautiful, I still remember that one.”	Ethnic or cultural music (Spanish), Guitar music, Vocal music
	“Like I said there was a Spanish piece and there was a piece that sounded more African.”	Ethnic or cultural music (Spanish, African)
2	“It was a song that is quite special to me, there was the one in Spanish, I knew what it was saying. It’s a very popular song, especially for people of my age.”	Ethnic or cultural music (Spanish), Familiar music
	“I think the one that I liked the most was the one in the beginning, sort of film-like music?”	Cinematic music

	“There was some sort of activity going on and a suspense, and I did like that one.”	Cinematic music
	“There was activity going on and at the same time some feeling of expected, which you would see in film, a soundtrack.”	Cinematic music
3	“At the end where there were more words, which was pretty good. I respect that maybe in the beginning I wouldn’t have appreciated that as much, when the drug was at its most intense.”	Vocal music
	“There was an “African” song, where, I think they’re singing about “our father” or something? And it was just a whole bunch of voices most of the time in the song, which was pretty good.”	Ethnic or cultural music (African)
	“There was one that just built up, [Greg Haines – Azure] was one example where in the beginning it just sounds like someone is just hitting sh*t randomly in his music room and then it all comes together in the end and blows your mind.”	Music with crescendo, powerful music
	“Those aspects of it where it’s like, slightly… surprising. It just builds up, and with it your emotion goes with that and the happy feeling, and its like all connected.”	Music with surprise
4	“[The soothing music] brought up nice images.”	Soothing music
	“The second time I sort of enjoyed crying to this music.”	Emotional music
5	“African-like music tapped into some deeper, more ancient part.”	Ethnic or cultural music (African)
6(2)	"I knew lots of the music."	Familiar music
	"I felt joy of the existence of Bach."	Classical or neo-classical music
7	“It began quite ambient-like, quite relaxing, which I felt was good. It calmed you in the experience.”	Ambient music
	“Arabian music was quite strong.”	Ethnic or cultural music (Arabic), Powerful music
	“With instrumental music [the story] is left to you.”	Instrumental music
	“I preferred ambient music, and more broadly I preferred the music without lyrics.”	Music selection
8	"Quite liked the sort of more operatic one, with the lady that sang in Italian."	Vocal music (female), Choral or opera-like music
	"Guitar playing, like a solo, I really liked that one."	Guitar music

	"Some parts being more energetic, and more sort of driven."	Energetic music
	"Other things being more quiet and subtle, and maybe encouraging reflection."	Calming music
9	“[Henry Gorecki – Symphony of sorrowful songs] starts off very nice chorally and then it goes off into a more kind of uncertain dark place and then comes back to the choral part again.”	Dynamic music, Choral or opera-like music
	“[Greg Haines - Azure] I felt like I was sort of the highest I could get, it was like the absolute, the top of everything.”	Powerful music
	“I thought ambient music would've resonated more with me than the rest”	Ambient music
	“I'm not a massive classical music fan, but the classical pieces that were there worked really well.”	Classical or neoclassical music
	“[Greg Haines - Azure] just builds and builds. You're holding on to an extent, you just kind of go up and you're like ‘ok, where am I? Can I go any further?’”	Music with crescendo
10	“It was more upbeat, so it was almost like it was arousing me from my slumber.”	Energetic music
11	“Indian music, where I was seeing an Indian temple.”	Ethnic or cultural music (Indian)
	“For me what worked best in the sense of being the most facilitative to the trip, were the straight on classical pieces.”	Classical or neo-classical music
	“I recognized a couple of pieces, those were very strong for me.”	Familiar music
	“During that same Indian piece, that’s when I was dancing for Shiva and then I was Shiva.”	Ethnic or cultural music (Indian)
	“Some Celtic music.”	Ethnic or cultural music (Celtic)
	“That’s just what I normally respond to.”	Familiar music
	“Pieces that had a solid drone to them drew me right in”	Drone music
	“The drone, it was the chanted repetition of that, it was the layering of the other voices and the other instruments and the other syncopation and the rhythm as they would all come in and just build.”	Drone music, Vocal music (chanting), Music with regularity, Music with rhythm, Music with crescendo
12	“The violin music, it was stunningly beautiful.”	Violin music, Classical or neo-classical music
	“[The violin music was] very beautiful. It’s one of my favourite kind of instruments.”	Violin music

13	“As the energy [in the music] kind of builds upward, it reaches a tension point.”	Music with crescendo
	“But at the same time I kind of think that the other higher intensity stuff is probably necessary, I think, to get you along.”	Powerful music
14	"Primitive and deep “African” music, it wasn’t particularly pleasant in any way, but extraordinarily powerful”	Ethnic and cultural music (African)
	“The Composer has stayed true to his or her own intuition or inspiration. Almost the antithesis to the Bach and the Brahms, which I felt were terribly contrived.”	Authentic music
	“There was something in the regularity, but also the pattern, the pattern of it. I seem to be responding to the patterns of the sound.””	Music with regularity
15	“One of the vocal tracks reminded me of one of Nusrat Fateh Ali Khan’s tracks, Yeni Yeniden, it’s so beautiful it just made me cry.”	Familiar music
	[interviewer: were there any ones that you had a particular preference for?] “Yeah, the classical pieces.”	Classical or neo-classical music
16	“There were some [that I preferred], a man’s voice. The experience changed when there was a voice, from when it was just music.”	Vocal music (male)
17	“I heard the beginning of one of my favourite pieces of music. Beethoven’s Emperor Piano Concerto, the second movement.”	Familiar music, Classical or neo-classical music
	“I preferred I suppose (chuckles) the sort of Classic FM stuff on the whole.”	Classical or neo-classical music
	“I suppose church-type music, I think was responsible for enhancing the religious experience.”	Choral or opera-like music
	“I think it was probably the great works of classical music that I preferred.”	Classical or neo-classical music
	“Great works of music by great composers, it’s normally expected to sort of move you more.”	Classical or neo-classical music
	“I think [classical music] was more moving.”	Classical or neo-classical music
18	“There was a woman’s beautiful voice.”	Vocal music (female)
	“There was a specific moment when I felt as though I was being given birth to the universe, and I semi-recall there was this sort of crescendo of music at that point, that was a very strong point in the journey for me.”	Music with crescendo
19	“The Mexican song I thought was quite good.”	Ethnic or cultural

		music (Mexican)
	"The Spanish guitar song was probably my favourite track out of all of them, with a man singing."	Ethnic or cultural music (Spanish), Guitar music, Vocal music (male)
	"It's a classical track that was on both [playlists]. Probably a bit overused in the media, but an emotive piece of music."	Classical or neo-classical music
	"Because I play guitar, and I can't play piano, I find guitar music more accessible."	Guitar music, music with personal connection
	"Like the kind of world music as well, it's more interesting."	Ethnic or cultural music

6.3.9 Appreciated music styles and playlist features: Playlist design

17 out of 19 patients (89% of total) made statements reflecting appreciation for the design of the playlist (Figure 6.2). Most prominent were positive descriptions of the "music selection", described by 12 out of 17 patients (71% of cluster), including descriptions of the music "working well" or being "well-selected". Secondly, 9 out of 17 patients (53% of cluster), provided positive descriptions on the way the music was structured into the full playlist. This theme, named "music order", is defined by statements of the "structure" and the "ordering" of the music playlist, "aligned" well with the drug-effects. The third most prominent theme, present in 6 out of 17 (35%), corresponds to the "music presence", meaning the mere presence of the music itself. This includes descriptions from the music being present as "helpful", to statements that it couldn't be imaginable doing the sessions without it and that the music presence felt "necessary". Finally, other themes include appreciation for "calming music" to be played mainly during "onset", "ascent" and "return" phases, whereas more emotive music (i.e. "sentimental" or "cinematic" music) to be better reserved for late in the "ascent" phase and during "peak" phase. See Table 6.9 for a full listing of all themes describing playlist design features that were appreciated.

Table 6.9 | Appreciated music styles and playlist features: playlist design. A list of all the themes and respective quotes by patients, that were present in the cluster “playlist features”.

#	Quote	Theme
1	“I liked that there was a lot of variety.”	Variety
	“Gentle at the beginning, I think that that did help.”	Calming music in pre-onset
	“Having the music in the background, it somehow just was helpful.”	Music presence
	“I think that that it was comforting, knowing that the music was there.”	Music presence
	“Variations in the degree of the music and the intensity of it. Some of it was more mellow, some of it more forceful.”	Variety
	“[The music] was structured in line with the way the effects of the drug were.”	Music order
	“I think that the music, because it was so varied I think it did kind of make you think a bit.”	Variety
2	“I think the one that I liked the most was the one in the beginning, sort of film-like music?”	Cinematic music in ascent-phase
	“I could see that there was a great effort to put the music together in a way that it followed the experience as it was meant to be.”	Music order
	“The fact that it was put together in that sequence made sense.”	Music order
	“[The playlist was] made in a sort of logical order. It had some sort of beginning, halfway through, and then the end, it was logical, it was good.”	Music order
3	“There was quite a variance.”	Variety
	“And most of it was good, because it was flipping good music.”	Music selection
	“It was all good.”	Music selection
	“I don’t know which one I’d say I prefer. I liked them.”	Music selection
	“[The music] had their moments for each time of the dosage.”	Music order
	“At the end where there were more words, which was pretty good. I respect that maybe in the beginning I wouldn’t have appreciated that as much, when the drug was at its most intense.”	Vocal music during return phase
	“In the beginning part, the uh, the Greg Haines stuff was, pffff.. f*%#ing, in another planet!”	Music with crescendo during peak phase
5	“[I preferred] the changes in style.”	Variety

	"I don't know if I preferred any one above the other."	Variety
6	"[The music] all worked really, really well."	Music selection
	"Even bits that I didn't necessarily love, it all flowed."	Music selection
7	"Certainly the first time [the music had a greater influence], cause I think the second time you're sort of familiar with the music."	Unfamiliar music
	"It began quite ambient-like, quite relaxing, which I felt was good. It calmed you in the experience."	Calming music in pre-onset phase
	"There was no uncertainty because of it, it didn't create any anxiety or 'woah, what is this?!'"	Music selection
	"[The songs] Superb they were without doubt you know."	Music selection
	"In terms of the musical choice I think it was absolutely superb."	Music selection
8	"Well-composed sort of selection."	Music selection
	"Well done, really well put together."	Music order
	"I think I could kind of understand what each part was meant to evoke."	Understanding thoughts behind playlist design
9	"[Buffy Saint Marry - Up Where We Belong] You could tell that was quite cheesy, a bit of an anomaly in there, but no, it just worked."	Music selection
	"It all worked together really well."	Music order
	"The music worked really well, within the context of the rest of the music and that setting."	Music order
10	"Whoever thought of putting that playlist together in the order that they did is a genius."	Music order
	"It was seamless- apart from the breaks. But after breaks they would put the headphones in and I would go straight back into that world."	Music order, music presence
	"Without it I would have gone mad."	Music presence
	"Certainly the experience would not have been a positive one were it not for that music."	Music presence
11	"[Some songs] I connected immediately with."	Music selection
12	"When there was a pause in the music it was really noticeable. It just felt that all the energy kind of drained out of the room, I really wanted the music back."	Music presence
	"There was one point, that was very beautiful."	Music selection
	"Wouldn't have been as positive without the music, absolutely, you know. No, a	Music presence

	hundred percent."	
	"I think it was designed that way."	Music order
13	"And particularly once it starts to mellow out towards the end, you do feel that more relaxed."	Calming music during return phase
	"[I preferred] more towards the end of the session, I think, whenever it's a bit more mellowed out. I kind of felt like a nicer place to be."	Calming music during return phase
	"The music is] definitely necessary."	Music presence
	"I wouldn't see any major changes with the music."	Music selection
	"I think it was a good, a good layout."	Music order
14	"I preferred Mendel's playlist."	Music selection
15	"An hour and a half before the end, when the music began to wind down, and it was at that point that I thought "oh yes, this is, this is much better. This is helping. Yeah, because I was slowly coming out. So yes, that was positive."	Calming music during return phase
	"One of the vocal tracks reminded me of one of Nusrat Fateh Ali Khan's tracks, Yeni Yeniden, it's so beautiful it just made me cry."	Familiar music
	[interviewer: were there any ones that you had a particular preference for?] "Yeah, the classical pieces."	Classical or neo-classical music
16	"I get the impression that if the music wasn't there it'd been a very different experience."	Music presence
	"There wasn't any that I didn't like. It felt like it all fitted the experience, and that everything was in the right order."	Music selection, music order
17	"I was able to just put the headphones on and the mask on, and really enjoy it."	Music selection
	"When the music stopped it was a very spooky atmosphere."	Music presence
	"I think it was the beauty of the music, and the sort of uplifting nature."	Music selection
18	"On the whole really lovely music, with obviously the dark music sometimes taking me to dark places, but I wasn't really aware of that at the time, it just sort of happened."	Music selection

6.3.10 Unappreciated music styles and playlist features: Music styles

11 out of 19 patients (58% of total) referred to musical styles that were not appreciated. These responses reflected different degrees of the individual's disliking of the music, and

were highly diverse, making no theme present in more than 30% of this cluster (Figure 6.2). Some examples of themes in this cluster refer to “music with lyrics”, “vocal music”, “piano music” “classical or neo-classical music” and “cheesy music”. Often, “vocal music” and “cheesy music” referred to one particular song played during the final “return” phase by Buffy Saint Mary, *up where we belong.* See Table 6.10 for a list of all themes present in the cluster of un-appreciated music styles.

Table 6.10 | Unappreciated music styles and playlist features: music styles. A list of all the themes and respective quotes by patients, that were present in the cluster “music styles”.

Un-appreciated music styles and playlist features: music styles		
#	Quote	Theme
4	“Very trippy music […] making me more scared when I had this difficult phase, that I was thinking ‘ah, I’m going crazy!’”	Trippy music
5	“It was all sad music.”	Sad music
	“It’s all very serious music, there was no light. It was all really, serious, profound.”	Serious music
7	“I found lyrics confusing.”	Lyrics
	“No interpretation, the story is being told to you… with lyrics, whereas with instrumental music it’s left to you.”	Lyrics
11	“I remember at some point saying “this music is really corny”, and there was one particular part where there was music going on that just reminded me of the ‘Sound of Music’, which our theatre in my little college town played for months, because that’s what the old folks in the town wanted to see, and it just had that sense of being that kind of kitsch almost.”	Cheesy music
13	“With a higher tempo everything feels a bit more tense.”	Music with high tempo
14	“I did struggle with the Brahms and the Bach.”	Classical or neo-classical music
	“Almost the antithesis to the Bach and the the Brahms, which I felt were terribly contrived.”	Classical or neo-classical music
	“I noticed I didn’t wanna hang around for the last hour, that version of Joe Cocker, ‘Love Lift Us Up’. I would consider that there was other music which is subtly more powerfully sort of joyous, rather than stating, claiming, ‘love will lift us up where we belong’.”	Music with lyrics, Cheesy music

15	"The piano pieces, irritated me. It was like little needles."	Piano music
	"I don't know why, I found the vocal pieces so amusing."	Vocal music
16	"I could remember hearing tracks that I'd heard before. I wasn't unaware, you know, because I could remember music from the last time. And I could remember how I felt when I'd heard that track the first time, which was another thing that I found for the second one, which was 'why is it not feeling the same?'"	Familiar music
17	"I didn't really like the sort of world music stuff."	Ethnic and cultural music
	"There was some sort of Indian-style music, I think I found it a bit creepy at the time."	Ethnic and cultural music (Indian)
	"There was a sort of ambient musical sound which I found too non-specific."	Ambient music
	"I complained a bit about the ambient music because I thought it was it was too downbeat. It wasn't sufficiently uplifting."	Ambient music
18	"There was a kind of out-of-place piano, that was almost sort of 'hunky-tunky', but that just didn't sort of fit really."	Piano music
	"[Henryk Gorecki – Symphony of sorrowful songs] It was a woman's voice, it was a sort of operatic voice, and first it was beautiful because, you know, I was following it and it took me to a beautiful place. And then there was almost a shriek that started, and that that perhaps that shrieking, that really high pitched, almost reaching the end of that particular song, that was when things started to turn for me."	Vocal music (female)
19	"I found the first [playlist] a bit of synthetic."	"Synthetic" music
	"Didn't like George Harrison or the Louis Armstrong. And there was that weird kind of cover [Buffy Saint Mary - Love Lifts Us Up]. It didn't feel bad, it just felt a bit cheesy, a bit annoying. It was a bit like forcing a point."	Cheesy music
	"Even though there was the opera stuff, I can't speak Latin, I couldn't understand it"	Music with lyrics in foreign language
	"I don't really understand opera."	Music without a personal connection
	"I think if you appreciate opera, Classic FM, you would have got something else out of it."	Choral or opera-like music, Classical or neo-classical music
	"Classical to me can be a bit inaccessible, a bit highbrow."	Classical or neo-classical music

	“Opera as well, because I don't understand the stories behind it.”	Choral or opera-like music, Music with lyrics in foreign language

6.3.11 Unappreciated music styles and playlist features: Playlist design

6 out of 19 patients (32% of total) referred to aspects of the playlist design that were not appreciated. In 2 out of 6 (33% of cluster), a clear disliking of the “music selection” was present, and a preference for “own music selection” was expressed (Figure 6.2). See Table 6.11 for a complete list of all themes present in the cluster of un-appreciated playlist design features.

Table 6.11 | Unappreciated music styles and playlist features: playlist design. A list of all the themes and respective quotes by patients, that were present in the cluster “playlist features”.

#	Quote	Theme
6	"The majority of them are not my kind of music, I can't sit with that music, I have to leave the room."	Music selection
	"It's music that I can't listen to, I find it irritating or agitating."	Music selection
7	“Second time, not as much [influence of the music].”	Familiar music
	“I would finish with more sort of ambient music rather than to try and bring the lyrics in.”	Lyrics during return phase
13	“Some of the earlier stuff did get a bit tense at times.”	Intense music during ascent
15	“I did ask if I could have my own music, I would probably have chosen my own pieces.”	Preference for own music selection
	“Less of the piano music.”	Piano music
	“Maybe the pieces could be slightly shorter.”	Preference for shorter pieces
17	“When the music stopped and it was a very spooky atmosphere.”	Silences in playlist
19	“There was stuff in the second playlist I didn't like as well.”	Music selection
	“Nothing I would have chosen if I wanted to relax.”	Preference for own music selection

	"Like the kind of world music as well, it's more interesting."	Preference for more ethnic or cultural music

6.3.12 Predictors in music-experience for psilocybin-experience and therapy outcomes

PCA reduced the dimensions of the 11-ASC to 5 factors, explaining more than 95% of total variance. These PC's are 1) "Peak experience" (loadings from "experiences of unity", "spiritual experience" and "blissful state"), 2) "Impaired cognition (loadings from "disembodiment", "impaired cognition" and "new meanings"), 3) "Audiovisual perception" (loadings from "audio/visual synaesthesia" and "elementary imagery"), 4)" Anxiety" (primarily loaded by "anxiety"), and 5) "Insightfulness" (loadings from "insightfulness" and "complex imagery") (see Figure 6.3). Subsequently, music-experience (liking, resonance, and openness) and drug-intensity scores, were correlated with these 5 factors and ratings for reductions in depression (1 week after psilocybin, and 6 months after psilocybin, defined by % reduction in QIDS score).

Reductions in depression one week after psilocybin were significantly predicted by the music-experience variables "liking" ($r = 0.60$, $p = .006$), "resonance" ($r = 0.59$, $p = .008$), and openness ($r = 0.57$, $p = .001$), but not by drug-intensity ($r = 0.004$, $p = 0.98$) or depression severity at baseline(measured by QIDS, *$r = 0.27$, $p=0.27$, $df=18$*).

Peak experience during the psilocybin sessions was significantly predicted by music-variables liking ($r = 0.61$, $p = .006$), resonance ($r = 0.67$, $p = .002$), openness ($r = 0.70$, $p = .0008$), and by drug-intensity ($r = 0.58$, $p = 0.009$). Insightfulness was predicted by music variables resonance ($r = 0.53$, $p = .016$) and openness ($r = 0.59$, $p = .007$), as well as by drug-intensity ($r = 0.65$, $p = 0.002$), but not by music liking ($r = 0.44$, $p = .06$). Impaired cognition ($r = 0.55$ $p = 0.01$), and audiovisual perception changes ($r = 0.71$, $p = 0.0006$) were only predicted by drug-intensity, and not by any of the music variables. Anxiety was not predicted by any of the variables. All reported significant p-values refer to FDR-adjusted threshold for significance of 0.016. Baseline depression severity (QIDS) did not show a significant correlation for any of the ASC-factors (peak experience, $r=0.11$, $p=0.66$, $df=18$; impaired cognition, $r=0.21$, $p=0.4$, $df=18$; audiovisual perception, r-0.05, $p=0.84$, $df=18$; anxiety, $r=0.3$, $p=0.2$, $df=18$; insightfulness, $r=0.08$, $p=0.74$, $df=18$). Finally, no significant correlation was found between severity of depression at baseline (QIDS) and music-variables liking (r=0.013, p=0.96, df=18), resonance (r=0.07, p=0.78, df=18) and openness (r=0.14, p=0.55, df-18)

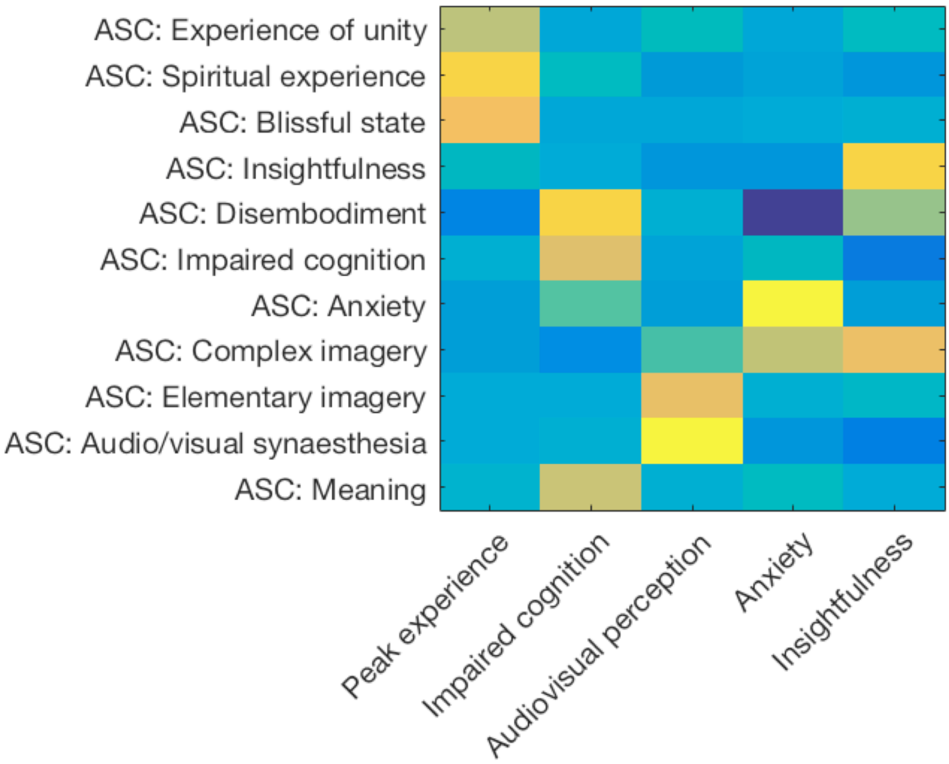

Figure 6.3 | Principle component analysis (PCA) of variables from the 11D-ASC. Loadings of the 11 dimensions of the ASC, on the first 5 PCs obtained from PCA followed by varimax rotation explained more than 95% of the variance. The x-axis shows the ordering of principal components, with the components ordered by explained variance (from left to right). The colour bar corresponds to the strength of the loading for each acoustic feature for that components: warm colours indicates a positive loading, and cold colours a negative loading.

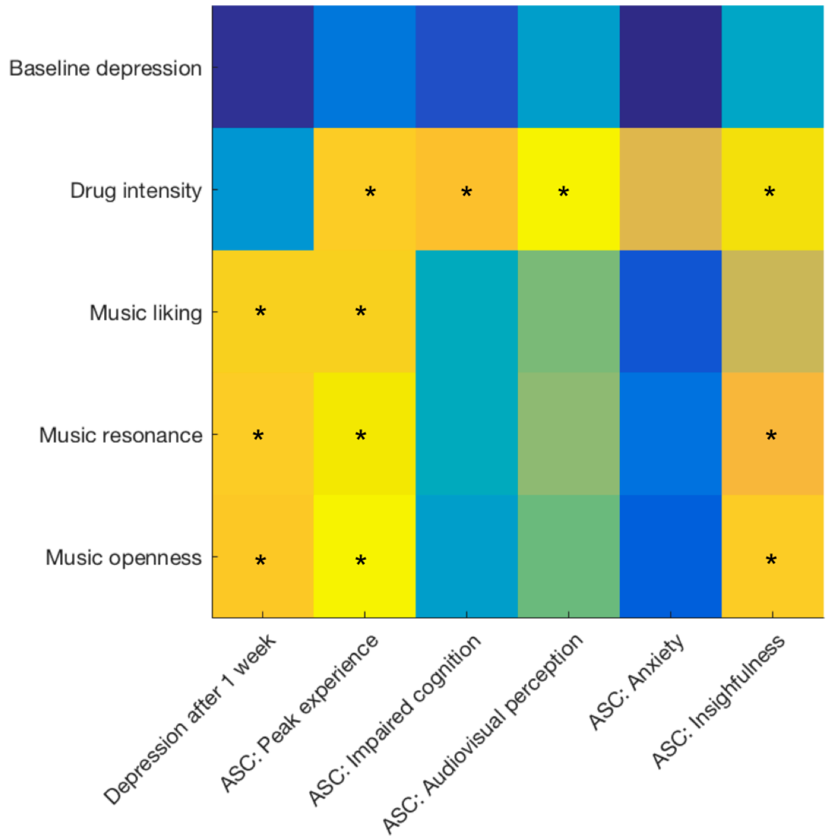

Figure 6.4 | Correlations between music-experience, and therapy-experience and outcomes. Outcomes of Pearson correlation tests between drug-intensity ratings, baseline depression scores and music-experience variables (on y-axis), with reductions in depression 1 week after psilocybin and the acute psilocybin-experience (5 PC's from ASC principle components) (on x-axis). * = $p < 0.05$, after FDR correction for multiple comparisons (FDR djusted $P = 0.02$).

6.3.13 Inter-rating reliability and discriminative validity of music-experience variables

Pearson correlation tests between the scores of all researchers (n=4) who rated the three music-experience variables (liking, resonance and openness), demonstrated good inter-rater reliability (average r = 0.6 ±0.1, from total of 18 correlations). Pearson correlation tests between the three music-experience variables showed significant correlations (r = 0.9, r=0.96, and r=0.91). Drug intensity did not correlate with any of the music-experience variables.

6.4 Discussion

This study reported marked effects of music on the subjective experiences of patients with major depression who underwent psychedelic therapy with psilocybin. Phenomenological analysis revealed several prominent influences of the music that were welcomed, including an intensification of emotions and of mental imagery, calming effects, and the music providing a sense of guidance. The music-experience was selectively associated with the occurrence of peak experience and insightfulness. The music-experience also predicted reductions in depression after psilocybin, whereas drug-intensity did not. Together, these findings suggest that music has a major influence on patient's experiences in psychedelic therapy, and that music may play an important function in facilitating positive therapy outcomes.

6.4.1 Music-experience

From all the themes identified, patients most frequently reported that emotions and mental imagery were intensified by music under psilocybin, and the study thereby complements the previous studies included in this thesis that demonstrated a modulatory influence of LSD on music-evoked emotion (study 1 and study 2) and music-induced imagery (study 3) in healthy volunteers. By focussing on detailing the phenomenology, the present study also provides new insights into other aspects of the music-experience. In addition to influencing emotion and mental imagery, the music was also often described as providing a sense of guidance within the experience, including feeling personally supported by the music (with the music serving to "ground" and "help" the listener), the music being "resonant" with the individual's intrinsic emotional state (the music being in tune or a good match with inner feelings), and the music bringing the sensation of being guided on a journey. In these scenarios, the music was frequently referred to as a “vehicle” that “carried” and “transported” the listener to different parts in their mind, rich with personally meaningful emotionality and imagery. “The sad songs would bring painful memories on, more happy songs would make me think of a really good period in my life. Every new song could bring a different image”, one patient (#4) remarked. One other patient (#14), provided a particularly good example of experiencing such welcomed intensification and guidance sensations from the music:

> “I feel the music in large part drove a lot of the experience. Under the influence of psilocybin, the music absolutely takes over. Normally when I hear a piece of sad music, or happy music I respond through choice… but under psilocybin I felt almost that I had no choice but to go with the music. […] I did feel I was being held. And it did feel like the music opened [me] up to grief, and I just was very happy for that to happen. It wasn’t particularly pleasant in any way, but extraordinarily powerful. It took my thinking and my experience to uncomfortable places, but I was kind of reassured in the experience. There was something there that meant “*I’m going to take you on a ride here, but I promise I won’t abandon you. It’s just going to be tough, and you know, you’re going through the grinder here, but you won’t be left in pieces*.” That seemed to be… what the music was saying to me”.

In contrast to the sense of (welcomed) guidance by the music, were descriptions of the music providing a sense of (unwelcomed) misguidance. In these situations, the music was typically described as being “dissonant” with the patient’s intrinsic emotional state: The music was perceived as being “out of tune”, “misplaced”, or as a “mismatch” with their inner emotions and thoughts. One example of the experience of misguidance by the music can be found in the response by patient #16:

> “The light music at one point took me to a place where I thought I was safe, and it became unsafe, and the music was playing a trick with me, you know, sort of giving me a false sense of security. I can remember thinking “*this is beautiful music, why am I going to this dark place?*” It didn’t line up with what had gone on before. I just felt as I was being manipulated, being duped almost. The music lured me to this beautiful

> place, and then things started to become dark even with this beautiful music still playing."

An important observation is that effects of the music that were welcomed, sometimes included emotions such as increased grieving or tearfulness. This attitude of openness towards "negative" music-evoked emotions, was frequently described as an important therapeutic aspect, to bring to expression and to find resolution in unresolved inner conflicts. These experiences were grouped under the theme "openness to challenging experience feels therapeutic", and one example of this attitude of openness towards the music can be found in the responses from patient #9:

> "I can even view the negative moments as positive in a way because they served a purpose. The purpose was to sort of let me face the darkness, and my demons, I guess. It was beautiful at times, but also… yeah, the darker moments really helped to reflect on and connect with your unresolved shadows."

Contrasting such an attitude of openness, is an attitude of resistance to the intensifying effects of the music. This experience was characterised by not wanting the music or its effects, and was named "resistance to intensification". An example of this is described by patient #5, who stated:

> "I worried that I let [the music] shape this sort of melancholy. There was resistance, massively, to everything, every sort of sensory input, I had a fearful response. I was afraid to open my eyes, I was afraid to do anything, I was afraid that this sort of music was the last thing I'd ever hear."

When taking these findings together, a diverse and mixed picture emerges of welcomed and unwelcomed influences of the music on patient's subjective experiences. Welcomed influences were characterised by often intense and personally meaningful emotionality and imagery, a sense of guidance by the music, calming effects, and an attitude of openness to the music-experience. On the other hand, unwelcomed effects of music were characterised by unwanted emotionality and imagery, feelings of discomfort and irritation, a sense of misguidance by the music, and an attitude of resistance to the music-experience. These findings suggest that in order for the music to act therapeutically, it may require a sufficient degree of resonance with the individual's intrinsic feeling state, and a sufficient degree of openness or receptivity to the resulting intensification effects. This hypothesis will be further discussed in paragraphs 6.4.4 and 6.4.5.

6.4.2 Music styles and playlist design

The present study did also shed light on the experience of different musical styles and the design of the music playlist. The choice of the music and the design of the music playlist was overall well-appreciated, with the most frequently appreciated musical genres being ethnic-, vocal- and (neo-) classical music. Appreciation was also expressed for the design of the playlist, in particular for the calming music to be primarily present during the early (pre-onset and early ascent) and the final (return) phases, and of the more emotive music to be reserved for the peak phase. This provides indirect support for previous frameworks, to structure the music according to its emotional intensity into different phases of drug-experience (Bonny and Pahnke 1972; Grof, 1980; Richards 2015). Strong disliking of the music-selection was rare (patient #6), but when this did occur it proved insightful into the role of music-selection: Typically, disliking of the music seemed to be associated with either a "diminishment" of the drug-experience, with unpleasant feelings (such as discomfort and irritation), and with an attitude of resistance, characterised by an attempting to distance oneself from the music, such as detailed in the following excerpt:

> "The music blocked my experience and feelings. A sense of irritation, frustration, and sense of lowering mood. The majority of the songs were not my kind of music, I can't sit with that music … I have to leave the room. I was sort of feeling bad, because I wanted to work with it. I sensed the potential for a really profound experience. I couldn't meet that potential with music that I felt was quite mediocre. To me it didn't feel real, so I felt quite torn. (#6)

In study1, a positive relationship between the liking of the music and the emotional response to music was shown, and such an association has been reported by other studies too (North and Hargreaves 1997). The present data does therefore suggest that the music style may require a sufficient degree of appreciation in order for meaningful emotionality to be evoked by the music, and thereby for the therapeutic process to be supported by the music. This hypothesis will be discussed further in the subsequent paragraph.

6.4.3 Music-experience predicts experience and therapy outcomes

As outlined above, this study found noticeable polarities in the music-experience, such as the music being either liked or disliked, the music being either resonant or dissonant with the patient's experience, and the patient being either open or resistant to the influence of the music. These three variables (liking, resonance and openness) positively predicted the extent to which patients reported having peak experiences (defined as the experience of unity, blissful emotionality and spirituality). In addition, resonance and openness, but not liking, predicted the extent to which people reported experiencing insightfulness (defined by having inventive ideas, feelings of profoundness, insights and the experience of vivid personal memories or mental images). Drug-intensity, on the other hand, also correlated with other aspects of the psilocybin-experience, such as impaired cognition and audio-visual perception changes.

The finding that the music-experience variables were selectively associated with peak experience and insightfulness, but not with other subjective experiences under psilocybin, supports the original motivations to include music in psychedelic-therapy, i.e. to promote the occurrence of personally meaningful experiences (such as peak experiences or autobiographical experiences) (Hoffer 1965; Bonny and Pahnke 1972; Grof, 1980). Modern studies have confirmed that psilocybin can reliably facilitate peak experiences (Griffiths et al., 2006; RolandGriffiths et al., 2011), and these experiences have been associated with sustained positive changes in behaviour and personality (MacLean et al., 2011), and with positive therapeutic outcomes (Garcia-Romeu, Griffiths, and Johnson 2014; Griffiths et al., 2016; Ross et al., 2016). Although all these studies incorporated music-listening in combination with psilocybin, this is the first study to demonstrate that the experience of music is related to the occurrence of peak experiences.

A positive relationship was found between the music-experience and reductions in depression one week after the psilocybin-experience. Importantly, reductions in depression were not related to the intensity of the drug-effects, and only to the music-experience variables liking, resonance and openness. This finding provides tentative support for the hypothesis that it is not merely the drug effects in isolation, but an interaction between the drug and the music that promotes therapeutic experiences and positive therapeutic outcomes. Due the prominence of music-listening in psychedelic therapy, understanding the therapeutic function of music in psychedelic therapy may be fundamental in maximising therapeutic efficacy.

6.4.4 Possible therapeutic mechanisms of music in psychedelic therapy

A principal effect of psychedelics is that they temporarily impair brain mechanisms that usually regulate emotion (Carhart-Harris et al., 2016, 2012; Muthukumaraswamy et al., 2013), and this could underlie the enhanced emotional responsiveness to stimuli reported here and elsewhere (Vollenweider et al., 2007; Quednow et al., 2012; Griffiths et al., 2006). Importantly, the emotional experiences to music in this study were not only described as more intense than usual, but as a “release” of meaningful psychological content (ex: autobiographical memories and deep tearfulness). The belief that accepting and moving through challenging emotions is important for psychotherapeutic change is central to many psychotherapeutic models (Greenberg, 2008), and has empirical support (Whelton 2004).

In psychedelic therapy, the function of psychedelics may be to bring about a quick relinquishment of psychological control (i.e. ego-dissolution), thereby allowing a fuller (i.e. less inhibited) expression of emotionality. The music, in turn, may play the important function of activating emotionality, thoughts and memories that are most personally significant, thereby guiding the patient’s experience into directions that are most therapeutically salient. The key difference between psychedelic therapy and other psychotherapies, may be the capacity of psychedelics and music to facilitate such emotional “breakthrough” experiences more quickly and with deeper emotional intensity. It may be specifically the interaction between the psychological state induced by psychedelics and music, that facilitated the acute and sustained changes in mood and behaviour reported in in this trial (Carhart-Harris et al., 2016) and several other studies (Gasser et al., 2014; Grob et al., 2011; Griffiths et al., 2016; Johnson et al., 2014; Johnson et al., 2016; Ross et al., 2016)

6.4.5 Implications for psychedelic therapy

The findings in this study show similarities with the therapeutic guidelines for music as it was developed by Helen Bonny and colleagues working with LSD in the 1960s, who referred to the therapeutic influence of music as being of "*profound significance"*. Bonny also emphasised the care needed in selecting the right music and playing the music at the right moments (Bonny and Pahnke 1972). The present study showed that when the music is dissonant (out of tune) with the experience, this was related to reduced therapy outcomes, whereas when the music was more resonant (in tune) with the patient's intrinsic feelings, this was predictive of better therapy outcomes. This finding provides support for the view that adapting the music to patient's individual and highly dynamic experiences under psychedelics may be critical to provide adequate therapeutic support. It also suggests a considerable responsibility on behalf of the therapists to use music appropriately, and the present study has provided some insight into how therapists may best do so to optimise psychedelic therapy sessions.

First, the musical style may require a sufficient degree of appreciation. Liking of music is usually defined as a mixture of genre-appreciation and aesthetic judgements (Juslin, 2013), and this factor may be an important pre-requisite for music to evoke meaningful emotionality. In addition, some musical styles and acoustic properties may be more suitable for the state of consciousness induced by psychedelics, than others, although this has not been studied yet. Secondly, when the music is liked, the music may still require an appropriate attunement to the inner emotional state of the patient. By being in resonance with the present emotional state of the patient, the music can enable him or her to better explore and express personal narratives more easily and deeply. In contrast, when music is dissonant, this may "block" such progress or may even become counter-therapeutic. Thirdly, the patient's attitude requires a sufficient degree of openness to the music-evoked experience. This openness may include not only a state of surrender, but also a pro-active focus and engagement together with the minimization of intellectualisation.

This hypothetical framework holds that if these three requirements are met (style liking, music's resonance and openness to music), an expression of meaningful therapeutic content could occur, often characterized by the sense of being on a personal journey, with a spontaneous and often intense emergence of personally meaningful imagery, thoughts and emotionality. If any of these pre-requisites is not met adequately, the patient is likely to distance him or herself from the music and the experience, and a rejection of meaningful therapeutic content could occur, characterised by feelings of discomfort, or the absence personally meaningful imagery, thoughts and emotionality (i.e. the absence of the sense of being on a journey).

Resolving any such resistance in these scenarios may be the responsibility of the therapist, such as ensuring music styles are sufficiently liked, via thoughtful music-selection, and ensuring the appropriate attunement of the music to the patient's unfolding experience, via thoughtful playlist-design and adaptation of the music when needed. In other scenario's, the music-evoked experience may be rich with therapeutically meaningful content, yet the experience may be highly unpleasant or in other ways emotionally challenging. In these scenarios, feelings of resistance may be due the patient wanting the experience to be different, and this may be resolved by the therapist's reassurance of their safety, and providing therapeutic support to explore these challenging feeling states. In this framework, resistance can be regarded as an important indicator of music's failure to act therapeutically, and the type of intervention needed to restore music's therapeutic function may be determined by one central question the therapist may need to clarify, i.e. *what is the source of resistance*? Is it due a disliking of music style, or due a dissonance of the music with the individual's experience, or due a resistance to therapeutically meaningful content?

6.4.6 Limitations and future directions

This study has a number of limitations. First of all, the data was acquired without a placebo-condition, making inferences about the effects of psilocybin on the experience of music problematic. Secondly, the main body of data used for this study was qualitative in nature.

Therefore, the experiment did not allow studying the magnitude of the observed effects of music. It should therefore be emphasised that the primary objective of this study was to provide a patient-perspective on the influence of music. We hope that the theoretical framework this provided, inspires testable hypotheses for future studies, and that it assists therapists and researchers in their use of music in psychedelic therapy. Example of such hypotheses are whether an optimisation of resonance/attunement, and the attitude of openness could improve therapy outcomes, and to what extend these variables are part of a similar construct or represent separate factors in larger sample sizes.

Furthermore, to advance the therapeutic use of music, a significant body of work is required to establish baseline measures that predict music-experiences during psychedelic therapy sessions. Such predictive measures can range from personality traits (e.g. openness to experience, absorption or suggestibility), to measures for music preferences at baseline. Furthermore, research that focusses on identifying reliably indicators for positive (welcomed/supportive) and negative (unwelcomed/unsupportive) influences of music on the therapeutic processes during psychedelic therapy sessions, may be highly significant for the development of psychedelic therapy, and the tools used during psychedelic therapy. These could range from simple physiological measures, such as heart-rate, body movement, and breathing patterns, or more complex measures such as facial affect-coding, vocal-affect coding, and EEG-signatures, that could inform therapists in on-the-fly adaptation of music-selection, or inform playlist generation algorithms.

6.4.7 Conclusions

Music was described as having a substantial influence on the therapeutic experience with psilocybin. The music-experience was predictive for peak experiences and insightfulness during the sessions, and reductions in depression after the sessions. This suggests that music may play a fundamental role in facilitating therapeutic change in psychedelic therapy. The findings support the usefulness of music in psychedelic therapy, but more research is warranted to better understand the therapeutic effects of music, including how music-use can be optimised for different types of psychotherapeutic experiences, as well as to investigate the specific therapeutic mechanisms.

"We should long ago have become angels had we been capable of paying attention to the experience of art, and allowing ourselves to be changed in accordance with the ideals it expresses"

Andrey Tarkovsky

7 Summary and discussion

The research presented in this thesis investigated how psychedelic drugs and music work together in the brain to change subjective experience, and how music is experienced during psychedelic therapy sessions by patients. Changes in brain function under LSD, as measured with fMRI, were associated with enhanced music-evoked emotion and music-induced imagery in healthy volunteers. In a separate study, the phenomenology of the music-experience was assessed in patients diagnosed with depression undergoing psychedelic therapy with psilocybin. This chapter will summarize and discuss the primary findings of these studies, and discuss possible brain mechanisms and therapeutic mechanisms of psychedelics and music. The primary research findings were:

- Enhanced music-evoked emotion under psychedelics.
- Altered processing of acoustic features by the brain under LSD, and in particular of "timbral complexity", which was associated with increased activity in brain networks previously implicated in music perception and emotion.
- Increased activation of the right inferior frontal gyrus (IFG) and right precuneus to "timbral complexity" under LSD was associated with increased music-evoked feelings of *wonder*.
- Enhanced information flow from the parahippocampus to the visual cortex was found with music in combination with LSD, and this effect correlated with increased ratings of complex mental imagery and ratings for autobiographical memories.
- Music has different influences on the subjective experience of patients undergoing psychedelic therapy with psilocybin, including an intensification of subjective experience, calming effects, and providing a sense of guidance.
- Music-experience (resonance of music with intrinsic emotion, and openness to music-experience) predicted insightfulness, and music-experience (liking of music style, resonance of music with intrinsic emotion, and openness to music-experience) predicted peak experience and reductions in depression.

7.1 Summary of qualitative findings

7.1.1 Effects of psychedelics on music-evoked emotion

Study 1 (Chapter 3) reported that healthy participants were significantly more "emotionally affected" by music under LSD than under placebo. In addition, both study 1 (Chapter 3) and study 2 (Chapter 4) reported on the implementation of the Geneva Emotional Music Scale (GEMS) to assess the effects of LSD on different types of music-evoked emotions. In both of these studies, the GEMS showed significant higher ratings under LSD for the music-evoked emotions "wonder" (filled with wonder, dazzled, moved), "transcendence" (fascinated, overwhelmed, feelings of transcendence and spirituality), "tenderness" (tender, affectionate, in love) and "power" (strong, triumphant, energetic). In addition to these types of emotions, chapter 3 also showed a significant increase under LSD for the emotions "nostalgia" (nostalgic, dreamy, melancholic), "peacefulness" (serene, calm, soothed), and "joyful activation" (joyful, amused, bouncy). Both studies reported no significant increases in music-evoked emotions of negative valence ("sadness" (sad, sorrowful) or "tension" (tense, agitated, nervous)). The findings reported in study 4 (Chapter 6) supplemented these findings by showing that the most frequently mentioned influence of music on subjective experience during psychedelic therapy sessions with psilocybin, was an "intensification of emotion", and that in the therapeutic context this applied to both positive emotions and negative emotions (e.g. tearfulness).

7.1.2 Effects of psychedelics on music-evoked mental imagery

In study 3 (Chapter 5), the neurophysiological correlates underlying LSD and music's combined effects on mental imagery were examined via rating scales during and after the neuroimaging procedures. During scanning, changes in eyes-closed mental imagery were assessed via ratings for simple visual imagery (i.e. colours and patterns) and complex visual imagery (i.e. concrete objects, landscapes or beings). Subsequently, the effect of LSD, of music, and of their interaction between the two, were assessed separately via a repeated measures ANOVA. Ratings for simple hallucinations were found to be increased under LSD, but no increase was found as an effect of music or as an effect of the interaction between music and LSD. Ratings for complex visual imagery were also found to be increased under

LSD, and a trend level significant increase in complex visual imagery was found as an effect of music, but no significant interaction effect was found between LSD and music. In addition, after fMRI scanning the participants completed a survey about their subjective experience inside the scanner, and a significant increase was found under LSD for the item that rated the spontaneous recollection of autobiographical memories: "I saw scenes from my past". These findings suggest that psychedelics do increase mental imagery, and that music may selectively modulate "complex" mental imagery, and not "simple" mental imagery. The qualitative analysis reported in study 4 (Chapter 6) showed that "intensification of the imagination" was one of the most prominently mentioned influences of music during psychedelic therapy with psilocybin for depression, which included descriptions of the music influencing the content of the mental imagery, as well as descriptions of the music making mental imagery more vivid. Study 4 (Chapter 6) also reported that the music-experience was associated with a factor called insightfulness, which was defined by having inventive ideas, feelings of profoundness, insights, as well as the experience of vivid personal memories or mental images.

7.1.3 Phenomenology of the music-experience during psychedelic therapy

Study 4 (Chapter 6) reported in detail on phenomenological themes presented in patient's descriptions of their subjective experience of the music while under the influence of psilocybin. The study showed that patients experienced "welcomed" and "unwelcomed" influences of the music, each including several prominent clusters of themes. The most frequently described welcomed influences of the music included an "intensification" of emotion and imagination, calming effects of the music, and of the music providing a sense of guidance. This sense of guidance included a sense of personal support, a sense of being "carried away" or "being transported on a journey", and a sense that the music was resonant or in tune with the patient's intrinsic emotional state. In addition, a recurrent theme included descriptions that an attitude of openness to the music-evoked experience felt like an important therapeutic element, and also that music itself can help facilitate such an attitude of openness to the music-experience.

In contrast, the most frequently described unwelcomed influences of the music were an intensification of (undesirable) or a diminishing of (desirable) emotions and imagery, and the music facilitating feelings of resistance (i.e. the opposite of openness) or a "sense of misguidance" (i.e. the opposite of "sense of guidance"). This sense of misguidance most often included the sense that the music was dissonant or not in tune with the present internal emotional state of the patient (i.e. the opposite of resonance).

Study 4 (Chapter 6) also reported on appreciated and un-appreciated music styles, showing that the most appreciated musical styles included ethnic music, neo-classical- and classical music, vocal music (non-lyrical), followed by ambient music. The liking and disliking of the music styles showed a remarkable diversity, but one compositional feature in the music that was found to be in particular appreciated was music with a build-up or "crescendo" or, contrastingly, music that helped to feel calm and secure. Music that was most disliked included music with lyrics, and music with high pitched sounds.

The music-evoked experiences were often described as personally meaningful. The degree to which patients described a resonance of the music with their underlying emotional state, as well as the degree to which patients described an attitude of openness to music-evoked experience, and a liking of the musical styles - these three variables were found to significantly predict the occurrence of 'peak experiences'. Resonance and openness, but not liking, were associated with experiences of insightfulness. All three variables predicted clinical improvements one week after psilocybin, whereas drug-intensity did not. These findings suggest important therapeutic functions of music during psychedelic therapy, which are discussed in more detail in section 7.4.

7.2 Summary of neuroimaging findings

7.2.1 The effects of LSD on the brain's processing of musical features

The fMRI study reported in study 2 (Chapter 4) investigated the effects of LSD on the brain's processing of distinct acoustic features of music under naturalistic listening condition in healthy volunteers. The study revealed widespread BOLD activity changes under LSD in cortical and subcortical areas to different acoustic features in the music, including music's fullness, brightness, timbral complexity, and others. Considered the most meaningful of these findings were the BOLD signal increases that were observed under LSD for the component timbral complexity. Not only because these changes were particularly marked, but also because these changes were localised to brain networks commonly identified for music-perception and music-evoked emotion. These include the bilateral auditory cortices, including the superior temporal gyrus (STG) and the planum temporale, right inferior frontal gyrus (IFG, also known as broca's area), right insula, precuneus, bilateral striatum and supplementary motor area (SMA). The significant BOLD increases under LSD in the planum temporale and in the IFG to timbral complexity were suggested to be of particular significance for understanding how LSD affects the brain's processing of acoustic features. Timbral complexity refers to the spread and the spikiness (hence, complexity) of the power-spectrum of auditory information (Toiviainen et al., 2014). The planum temporale is argued to be specialised in analysing these spectral properties in sound by segregating them into distinct spectrotemporal patterns (Griffiths and Warren 2002a). Subsequently, the planum temporale (together with other auditory cortices such as the superior temporal gyrus (STG)) forms a circuit of information exchange with the IFG (Kumar et al., 2007, 2016). This circuitry is found to be important for auditory perception and music perception (Zatorre and Salimpoor, 2013b). In addition, the psychophysiological interaction (PPI) analysis demonstrated a significant decoupling of the precuneus from this circuitry (i.e. the right auditory and IFG) to the timbral complexity. Together, these findings suggest that a major effect of LSD is to change the brain's processing of music's timbral or spectrotemporal content via modulating a neural circuit encompassing the planum temporale, the STG and the IFG, and by functionally decoupling this circuit from the precuneus.

7.2.2 Neural correlates of LSD and music-evoked emotion

Following the neurophysiological measures in study 2 (Chapter 4), the changes in music-evoked BOLD activation were related to changes in music-evoked emotion measured by the GEMS via correlation analyses. These analyses were performed between increases in music-evoked emotions "wonder" and "transcendence" (LSD > Placebo) and increases in music-evoked BOLD activation to timbral complexity (LSD > Placebo) for nine regions of interest (ROIs). Only changes in music-evoked feelings of "wonder" and "transcendence" were included in this analysis, because these are typically associated with peak experiences

(Maslow 1971, 1964; Richards 2015). Psychedelic peak experiences occurring under music-listening conditions have been related to enduring positive behaviour change (MacLean et al., 2011; Griffiths et al., 2011) and therapeutic outcomes (Johnson et al., 2014; Griffiths et al., 2016; Ross et al., 2016). The nine ROI's were pre-defined based on their implication in music-perception, music-evoked emotion and the effects of psychedelics, by previous literature and by their increased activation to timbral complexity under LSD in the present study. These included right and left planum temporale (Griffiths and Warren, 2002a), precuneus (Muthukumaraswamy et al., 2013; Carhart-Harris et al., 2016; Trost et al., 2012), the striatum (right and left putamen, right and left caudate) (Salimpoor et al., 2011; Blood and Zatorre, 2001), right IFG (Zatorre and Salimpoor, 2013b; Koelsch and Friederici, 2003; Koelsch et al., 2002), and right anterior insula (Trost et al., 2012; Koelsch 2014).

Significant positive correlations were found between increased music-evoked feelings of wonder and music-evoked BOLD activation to timbral complexity within the precuneus and within the right IFG. A trend-level positive correlation was detected between increased music-evoked feelings of transcendence and the right IFG. Despite previous literature that associates the striatal system with music-evoked emotion (Salimpoor et al., 2011; Blood and Zatorre, 2001), and the significant bilateral increases in BOLD activation observed in the striatum to timbral complexity under LSD, none of these striatal regions were associated with increased music-evoked emotions of wonder and transcendence. Instead, the findings suggest that music-evoked emotions of wonder and transcendence are enhanced to music's timbre properties under LSD via functional changes occurring in high-level association cortices (IFG and precuneus).

A body of previous research has implicated the IFG in evaluating emotional valence in music and speech (Frühholz and Grandjean, 2013; McGettigan et al., 2013), and the syntactical analysis of auditory information (Koelsch 2006; Maess et al., 2001; Patel 2003; Tyler et al., 2011). Timbre is an important acoustic feature for conveying emotionality in voice and music (Hailstone et al., 2009; Eerola et al., 2012), and the present study suggests that LSD increases the emotional response to music via modulating the way brain networks process the timbre of music.

7.2.3 Neural correlates of LSD and music-evoked mental imagery

In study 3 (Chapter 5), a seed-based functional connectivity analysis with the bilateral parahippocampus (PHC) was reported, showing increased functional connectivity of the PHC with the left IFG, the left insula and the visual cortex (VC) during music listening under LSD. Subsequently, a dynamic causal modelling (DCM) was implemented to assess changes in effective connectivity (i.e. the direction of information flow), and this analysis revealed a positive modulation (i.e. an increase) of effective connectivity from the PHC to the VC by an interaction-effect between LSD and music. The magnitude of this modulation positively correlated with increased ratings for eyes-closed “complex” mental imagery and ratings for the item “I saw scenes from my past”. These findings are consistent with evidence that implicate the PHC-VC network in the construction of mental visual images (Chadwick et al., 2013; Zeidman et al., 2014; Barbeau et al., 2005; Bartolomei et al., 2004), and suggest that psychedelics and music interact to enhance autobiographically relevant complex mental imagery via increasing information flow from the PHC to the VC.

7.3 Possible brain mechanisms of psychedelics and music

This paragraph will outline hypothetical brain mechanisms via which psychedelics and music possibly work together to change subjective experience. This model will be formulated within the framework of predictive coding - a mechanistic account that describes perception as the creative process of the brain to statistically match (i.e., predict) incoming information with prior learned representation (i.e. predictions). These predictions are derived via experience, and represent learned representations, beliefs and expectations. These are matched with incoming information in a top-down fashion, and this process is believed to occur at all stages of the processing hierarchy (e.g. in the context of auditory perception: all the way from the cochlea, to auditory cortices, to multimodal cortices). Perception in the context of predictive coding comprises a continuous updating of the brain’s internal predictive models of the world based on the accuracy of its predictions (i.e. via a bottom-up signalling of *prediction errors*) (Bastos et al., 2012; Apps and Tsakiris, 2014).

LSD activates serotonin 2A receptors (Halberstadt and Geyer, 2010), which are predominantly expressed on deep-layer V pyramidal neurons (Béïque et al., 2004; Aghajanian and Marek, 1999; Celada et al., 2013). These deep-layer V pyramidal neurons provide predictions via backward projections to subordinate (hierarchically lower) brain regions (Bastos et al., 2012). Serotonin 2A receptor activation by LSD increases the firing-likelihood of the deep pyramidal neurons (Aghajanian and Marek, 1999), arguably leads to an un-coordinated or an "entropic" activation of the predictions encoded by these neurons.

A state of "hyper-activation" of prior predictions has previously been argued to lead to a "perceptual inference in the absence of sensory evidence" (Adams et al., 2013). Studies have linked deficient predictive coding in the auditory cortex with auditory hallucinations (Horga et al., 2014) and musical hallucinations (Kumar et al., 2014). The planum temporale is considered an important computational hub to segregate complex spectrotemporal information (Kumar et al., 2007; Griffiths and Warren 2002a), and altered functioning of the planum temporale has been related changes in auditory perception (Looijestijn et al., 2013; Leveque et al., 2016). The marked BOLD increases under LSD observed in the planum temporale to music's timbral complexity may therefore indicate increased activation of deep-pyramidal neurons that encode predictions for the music's spectrotemporal (timbral) information. Although the present study did not formally address effects of LSD on acoustic perception, increased activation of deep pyramidal neurons in the planum temporale to timbral complexity under LSD may yield significant changes in auditory perception and this may be one route via which psychedelics alter the subjective experience of music (from altered perception to altered emotionality).

Serotonin 2A receptors are densely expressed within the insula and the IFG (Erritzoe et al., 2010; Ettrup et al., 2014; Beliveau et al., 2017), and overstimulation of the deep-pyramidal neurons expressing serotonin 2A receptors in these regions could result in the auditory cortex (planum temporale and STG) to receive increased top-down predictions from these higher regions. There is evidence for a selective role of timbre features to convey emotion (Hailstone et al., 2009; Eerola et al., 2012), and for the insula and IFG playing a key role in detecting emotional valence in sound (Frühholz and Grandjean, 2013; McGettigan et al., 2013), and more generally in processing and regulating emotions (Craig 2009; Gu et al., 2013). The marked BOLD activation to timbral complexity in a network encompassing the auditory cortex, the IFG and the insula, may therefore reflect a "hyper-associative" matching of the brain's emotional interpretations (predictions) with activated acoustic representations.

Mechanistically, this may be instantiated via increased input into the auditory cortex from projections originating in the IFG and insula that encode learned representations for emotional meaning in sound.

Study 2 (Chapter 4) also reported a functional decoupling of the auditory/IFG circuitry from the precuneus, and this was interpreted as reduced top-down regulation of the precuneus over activity in the auditory/IFG circuit. The precuneus is significantly functionally affected by psychedelics alone (Carhart-Harris et al., 2014; Muthukumaraswamy et al., 2013; Carhart-Harris et al., 2016), and given the significant role of the precuneus in regulating and coordinating global brain function (Fransson and Marrelec 2008; Cavanna and Trimble 2006), disrupting it's capacities to do so may lead to an unconstrained or "entropic" processing of information in subordinate brain regions. In the present context, this may be the case for the processing of timbre features in music in the auditory/IFG circuitry. Activation of this circuit, with simultaneous de-coupling from the precuneus, may subsequently lead to a disinhibited processing of musical information, and hence a more intense subjective experience of this musical information.

The precuneus is also densely connected with the visual cortex and medial temporal lobes (including the PHC) (Zhang and Li 2012; Cavanna and Trimble 2006; Ward et al., 2014). In a similar fashion as for the auditory-IFG circuit, the reported enhanced top-down PHC->VC information flow under LSD and music may be consequential of a temporary "lifting" of the usual top-down control from the precuneus, yielding an unregulated spread of activation of learned representations. The VC and (to a lesser extend) the PHC (entorhinal cortex) express significant levels of serotonin 2A receptors (Beliveau et al., 2017; Erritzoe et al., 2010), and research implicates the PHC->VC pathway in the construction of complex mental images (Zeidman et al., 2014; Chadwick et al., 2013; Barbeau et al., 2005). This finding may indicate an increased activation of top-down projecting deep-pyramidal neurons within the PHC that encode (complex) visual mental representations (i.e. "concrete" images) and autobiographical scenes, to the visual cortex.

The notion that psychedelics facilitate a temporary "collapse" of the usual hierarchy of brain function is receiving increasing empirical support from studies that report effects of psychedelics under resting state (stimulus-free) conditions (Carhart-Harris et al., 2014; Tagliazucchi et al., 2014, 2016). The studies presented in this thesis are the first to illustrate that such an effect may have dramatic consequences when the brain is subsequently exposed to emotionally salient stimuli, such as music. The model outlined in this paragraph, aimed to provide a mechanistic explanation for the intensified subjective experience of music under psychedelics, but more research is warranted to test these hypotheses empirically. How these findings and these hypotheses can inform an empirical framework for their therapeutic use will be the focus of the subsequent paragraph.

7.4 Implications for psychedelic therapy

As was reviewed in the introduction chapter of this thesis (Chapter 1), one major motivation for introducing music in psychedelic therapy in the 1950s and 1960s was its purposed capacity to modulate emotionality and mental imagery, as well as its capacity to provide a sense of calm, direction and continuity within the experience ((Chandler and Hartman, 1960; Hoffer, 1965; Bonny and Pahnke 1972; Grof, 1980). The findings presented in this research are to author's knowledge the first to provide empirical support for these motivations within a modern scientific framework, and to ground the therapeutic work within a neurobiological understanding. This section will summarise some of the central implications that these findings have for psychedelic therapy: The possible therapeutic functions and mechanisms of psychedelics and music in combination, and how music may best be used during psychedelic therapy sessions. Its aim is to provide a theoretical framework of which it is hoped it will help to better understand and employ the therapeutic actions of music in psychedelic therapy.

7.4.1 Possible therapeutic functions of music

There are several important observations with regard to the possible therapeutic functions of music in psychedelic therapy. First, a growing body of evidence associates peak experiences during psychedelic therapy with positive therapy outcomes (Garcia-Romeu, Griffiths, and Johnson 2014; Griffiths et al., 2016; Ross et al., 2016). One motivation to introduce music in psychedelic therapy was its capacity to facilitate peak experiences (Bonny and Pahnke 1972; Kurland et al., 1971; Hoffer 1965; Richards 2015), and the present findings support this. The findings reported in chapter 3 and 4 suggest music may help facilitate peak experiences by evoking emotions that are typically associated with peak experiences, such as feelings of wonder and transcendence. Furthermore, chapter 6 showed that from the diverse subjective experiences patients can report under psilocybin (ranging from increased emotionality, audio-visual effects, to anxiety and cognitive impairments), the music-experience was selectively predictive for peak experiences (feelings of union, bliss, and spirituality) and insightfulness (having innovative ideas, a sense of profoundness, and experiencing vivid personal memories). This is important, as it indicates that music can be effective in engendering specific emotionally charged experiences that hold particular therapeutic meaning and potential value, and that music may thereby play an important role in driving positive therapeutic outcomes in psychedelic therapy. The finding in chapter 6 that it is *not* the mere intensity of the drug-effects, but *the quality of the music-experience* that is predictive for positive therapy outcomes, provides further support for this view.

Secondly, early researchers reported that LSD has “the astonishing quality” to re-activate patient's “repressed emotional attitudes" (Feld, Goodman, and Guido 1958), and that “frequently whole sequences unroll before the patient's eyes as though they had been stored on microfilm” (Eisner and Cohen 1958). One important motivation to introduce music in psychedelic therapy was to promote a “deeper involvement” with these autobiographical processes (Grof, 1980), and the findings of this thesis support this motivation too. The findings presented in chapter 4 indicated that psychedelics and music modulate mental imagery, by revealing a relationship between enhanced PHC→VC information flow in healthy volunteers, and enhanced complex mental imagery (i.e. concrete objects, beings or landscapes) and autobiographical. Interestingly, this association was only found for complex visual imagery, and not for simple visual imagery. Accordingly, in chapter 6, the music-experience during psychedelic therapy sessions was predictive for insightfulness, a factor that included loadings from items capturing the experience of vivid personal memories, but *not* simple mental imagery (audio-visual synaesthesia or elementary imagery). Together these findings suggest that one other function could be to shift the focus within the eyes-closed visual experience, towards imagery that is particularly autobiographically “insightful”, and hence particularly therapeutically meaningful.

Finally, for many patients, music was found to be helpful in providing states of calm, comfort, and security. Related to this are the feelings of guidance attributed to the music, such as feeling personal helped by the music, and the music being grounding and reassuring. These securing/calming effects were found to be particularly appreciated in situations where apprehensions were present, such as prior to the onset of drug-effects, or when mental calm and “clarity” was required, such as after emotionally intense periods. These findings suggest that one other function of music may be to provide a sense of calm, security & guidance - a function that may form an important contrast with the previously described evocative (i.e. intensifying) influences of music.

The findings in these studies show a remarkable congruency with theoretical frameworks and patient-experiences of “introspective” forms of music therapy, where music is utilised as the means to provide an experience -emotionally and mentally- that is thought to help the listener to examine and change the relationships with themselves (Abbott 2005; Summer 1992; Albornoz 2013). This includes using music to evoke intense emotional experiences (Albornoz 2013), as well as a way to provide a “holding environment”, that feels “safe and secure” to express and experience new aspects of oneself (Carroll 2011; Schulberg 1999). Anxiety- and tension-reducing effects of music are widely reported in literature and utilised across different health care disciplines (Finch and Moscovitch 2016; Pavlov et al., 2017; Mondanaro et al., 2017).

Taking these findings together, it can be concluded that music can modulate subjective experience in psychedelic therapy in profound and functional ways, and that the therapeutic functions of music in this context may be generally classified into two distinct categories:

1) A directive/suggestive function, characterised by the music being arousing/activating (emotionally, bodily and mentally), and the listener becoming fully *immersed* into the music-experience (E.g. the music furthering ego-dissolution). Directive music may be seen as to provide non-verbal “suggestions” that the listener can personally identify with and follow. Once surrendered to the perceived suggestions of the music (i.e. open to the music-evoked experience), the experience unfolds as a “journey”, rich with personally meaningful thoughts, emotionality and imagery. This function may be especially important to facilitate an expression or “release” of (previously) previously suppressed psychological content and emotionality. Music styles that may be particularly suitable for this function are emotive or cinematic music styles, such as for example (neo)classical music and ethnic music styles.

2) A non-directive/non-suggestive function, characterised by the music being calming (emotionally, bodily and mentally), and the listener becoming more relaxed and present in the here and now. This function may be especially important to facilitate a sense of security, that subsequently facilitates an attitude of openness to the experience, as well as to create an environment that allows contemplation and interaction, with oneself or with the therapist (i.e. the music furthering ego-(re)integration). Music styles that may be particularly suitable for this function are ambient or other "non-musical" styles that focus on creating an acoustic ambience, a climate, rather than to a dynamic musical experience that demands attention. In the words of the ambient music pioneer Brian Eno:

> "Ambient music is intended to induce calm and a space to think. Ambient music must be able to accommodate many levels of listening attention without enforcing one in particular; it must be as ignorable as it is interesting."
> – Brian Eno (1978)

Technically speaking, one may argue that here is not such a phenomenon as non-directive/non-suggestive music, since any stimulus will have a capacity to trigger emotional-mental associations, and hence induce psycho-behavioural changes in the listener. Non-suggestive music may indeed, in reality, be suggestive of for example calmness and security. Yet, how the two functions differ, is in the "coerciveness" of the suggestion. Where non-directive/non-suggestive music can be "as ignorable as it is interesting", directive/suggestive music can be seen as more or less un-ignorable, and does not give "space to think", but instead requires a full *surrender* to the direction or suggestion that the listener perceives in the music.

7.4.2 Possible therapeutic mechanisms of psychedelics and music

The presented research did not directly study therapeutic mechanisms of psychedelics and music, but provided important clues as to *how* and *why* psychedelics and music may act therapeutically in combination. Indeed, the two-fold functions of music as defined above raise the question *why* such musical experiences would be therapeutic. One key finding of this research, is that the music-experience seems to be substantially intensified under psychedelics, and that this can evoke meaningful, but also sometimes challenging emotional experiences. An open and interactive attitude towards these music-evoked experiences was frequently described as being important in finding therapeutic resolution, and “openness” to the music-evoked experience correlated with reductions in depression. This section aims to consolidate these findings into a theoretical framework, based on neuroscience and psychotherapeutic thinking, that proposes the therapeutic mechanisms via which psychedelics and music possibly work together.

An important function of the brain is to maintain homeostasis (i.e. balance), and to acquire learned representations (i.e. predictions) that guide this process effectively (Seth and Friston 2016). Throughout life, the many learned representations are assembled into a complex inner working model, that functions (to introduce a simplifying analogy) like an *inner-roadmap*: it determines how information is processed, what it means, it informs behaviour, and produces a coherent sense of self or identity (Apps and Tsakiris 2014; Carhart-Harris and Friston 2010). The main purpose of this inner roadmap, is to help *the self* survive and thrive in a highly complex and always-changing world. Yet, it can also be this inner roadmap, or the use of it, that is the source of psychological suffering, and which individuals seek to change when seeking help in psychotherapy (Young, Klosko, and Weishaar 2006; Beck and Beck 2011). Subsequently, it is goal of all psychotherapies “to influence the client in such a way” (Yapko 2001) so that new aspects of oneself and new ways of experiencing oneself are discovered and re-assembled into a new self-concept, an updated roadmap (Joyce and Sills 2014; Young, Klosko, and Weishaar 2006; Beck and Beck 2011; Rogers 1996; Black and Mitchell 1996).

Deeply feeling and expressing challenging emotions is argued to be important for psychotherapeutic change (Whelton 2004), and this aim is central to many psychotherapeutic models (Greenberg and Pascual-Leone 2006). Some research has indicated that the patient’s level of experiencing emotions (i.e. its “depth”) during therapy sessions, is predictive for positive therapy outcomes (Hendricks, 2002; Orlinsky et al, 2004; Greenberg et al., 2002). Psychedelics temporarily disorganise the brain’s functional hierarchy (Carhart-Harris et al., 2016, 2012; Muthukumaraswamy et al., 2013), and this *dissolving of the usual roadmap* (i.e. ego-dissolution) has been argued to underlie the intensified subjective response to music under psychedelics (summarized in paragraph 7.7.2). In line with many earlier researchers (Eisner and Cohen 1958; Busch and Johnson, 1950; Hoffer 1965; Butterworth 1962; Feld, Goodman, and Guido 1958; Kurland et al., 1971), these findings suggest that a central therapeutic function of psychedelics is to provide a rapid relinquishment of emotional control, so that emotions can be aroused and expressed to a fuller extent.

This effect of psychedelics, however, is considered unspecific, leading to a wide spectrum of possible subjective experiences (Grof, 1980). In the absence of the usual roadmap, music in this context may play the important role of a "road-navigator", guiding the experience (either in directive or non-directive ways (see paragraph 7.4.1)) into territories beyond the usual road-map (beyond the usual boundaries of the self), to remember or experience new aspects of oneself that are most therapeutically significant (characterised by the qualities of autobiographical- and/or peak experience (see paragraph 1.4.1 and paragraph 7.4.1)). Subsequently, newly acquired self-representations (new routes or guidelines) can be assembled into an updated working model (an updated inner-roadmap)- or, as the pioneering humanistic psychologist Carl Rogers formulated, an *altered self-concept*:

> "To perceive a new aspect of oneself is the first step toward changing the concept of oneself. The new element is, in an understanding atmosphere, owned and assimilated into a now altered self-concept. This is the basis, in my estimation, of the behaviour changes that come about as a result of psychotherapy, Once the self-concept changes, the behaviour changes to match the freshly perceived self"(Rogers 1996)

7.4.3 The unique therapeutic value of music

Compared with other psychotherapy modalities, psychedelic therapy is unique in its capacity to facilitate rapid and sustained therapeutic changes (Ross et al., 2016; Griffiths et al., 2016; Carhart-Harris et al., 2016; Gasser, Kirchner, and Passie 2014, 2015; Grob et al., 2011; Bogenschutz et al., 2015; Johnson et al., 2014; Johnson et al., 2016). The promising effectiveness of psychedelic therapy may be due its focus on providing a deeply felt and personally meaningful *experience*, rather than conventional mental health treatments, that tend to focus on changing cognition, behaviour, or neurochemistry (see Chapter 1.6). Experiences are the basis for implicit learning, and implicit learning is the foundation for any behavioural change. The studies in this thesis indicated that music can help engender implicit-learning experiences that may be particularly therapeutic significant.

There may indeed be other means than music to facilitate meaningful experiences, and more generally, to fulfil the therapeutic objections discussed above; but the unique value of music in this context may be 1) its capacity to convey emotional experiences that are *dynamic* (time-based), and 2) do so without the use of words. The significance of this can be conceptualised through the process of "affect attunement" - a term formalised by the developmental psychologist Daniel N. Stern. Stern argued that the very first interpersonal world of human experience, that of the infant interacting with his or her mother, is in essence *a musical relationship*. Affect attunement refers to the matching of the mother's non-verbal expressions (the changes in intensity and tonality of her voice), with the infant's behaviour. Affect attunement does not imply the providing of perfect mirror-image of the infant's experience, but the providing of a reflection in a different modality (i.e. sound), of the dynamic contours of the infant's internal feeling-states (Stern 1995, 1998).

According to Stern "for the infant, the music comes before the lyrics", and "the entire flow of maternal social behaviors can be likened to a symphony, in which the musical elements are her changing facial expressions, vocalizations, movements, and touches" (Stern 2010). Affect attunement is believed to guide the awareness of the infant to the subjective basis underlying his or her own behaviour, while maintaining a sense of being securely held and "contained" by the caregiver. Mother-infant interactions are present cross-culturally (Trehub and Trainor 1998), and are argued to promote emotional learning (Licata, Kristen, and Sodian 2016; Schore and Schore 2007; Thompson 1991).

In psychedelic therapy, the therapeutic actions of music may resemble the process of mother-infant affect attunement. Here, music can be seen as a non-verbal (or even pre-verbal) language, that provides an attunement to dynamic internal feeling states of the listener, thereby facilitating emotional learning experiences, while simultaneously providing a sense of being securely held and supported. By dramatically enhancing the usual subjective response to music, psychedelics may create a unique therapeutic opportunity for the music-experience to become deeply experiential (i.e. the listener becomes fully *immersed* in the music). Importantly, the musical (non-verbal) language is entirely process-based, as opposed to content-based (example: movies). This may be particularly important, as music can thereby can reflect and activate intrinsic feeling states (i.e. the processes conveyed by the music), while allowing the specific autobiographical content to be spontaneously associated with the music by the mind of the listener. As the classical composer Richard Wagner eloquently formulated:

> "What music expresses, is eternal, infinite and ideal: it does not express the passion, love, or longing of such-and-such an individual on such-and-such an occasion, but passion, love or longing in *itself*, and this it presents in that unlimited variety of motivations, which is the exclusive and particular characteristic of music, foreign and inexpressible to any other language". – Richard Wagner, quoted by Anthony Storr in *Music and the Mind (Storr 1997)*

7.4.4 Implications for using music in psychedelic therapy

The findings suggest several implications for therapists working with music in the context of psychedelic therapy. The ability of music to evoke meaningful therapeutic experiences was discussed as a mixed function of (1) the patients' liking of the music styles, (2) the music being in resonance or in tune with the patient's dynamic feeling states, and (3) an attitude of openness on behalf of the patient to the resulting music-evoked experience. Resistance was suggested to be an important indicator of the patient rejecting the music, and thereby hindering therapeutic progress. Here, resistance was defined as a distancing of the music and its influences, and was often characterised by an intellectualisation of the experience, by feelings of discomfort, irritation, fear, and a by general sense of the experience being diminished or blocked by the music. This experience can be seen as the opposite of the often-reported music-evoked sense of being on a journey (characterised by the dispensing of intellectualisation), which was associated with a welcomed music-experience.

The findings do suggest that resistance should not be merely understood as an inability of the patient to open up, but that it could occur for different reasons, and hence require different interventions:

1) The music may be rejected because the experience it evokes is challenging, yet the experience may hold therapeutic significance (e.g. the music may remind the listener of a deceased loved-one, and the resulting emotions may feel too overpowering).

2) The music may be rejected because of a disliking of the music style (e.g. a lack of personal connection with the music style, or finding the music aesthetically abrasive).
3) The music may be dissonant (out of tune / a mismatch) with the patient's internal feeling states (e.g. the individual undergoing a deep sensation of grief, and the music being joyful).

An attitude of openness to the music-evoked experience could be optimised via adequate preparation prior to the therapy session. This would include an encouragement of full *immersion* into the experience, and a curious and interactive engagement with the experience even in situations when it becomes challenging. The aid of music-listening exercises prior to therapy sessions have as yet not been explored, yet may be an effective way to prepare a mind-set conducive to immersion. Such exercises might also provide the therapist with some idea of music styles that may work best for the individual patient.

Dialogue may determine the right response to resistance as it arises during a session. When it occurs in relation to therapeutically meaningful psychological material, a constructive relationship with the experience can be increased via a reassurance and reminder of safety and personal support, an encouragement to explore the experience interactively.

In contrast, when the music is rejected due disliking of the music styles, and or when the music is dissonant with the patients underlying emotional state, the therapist may need to take action. Analogous to usual client-centred dialogues in psychotherapy, where the therapist listens attentively and reflects back to the patient his or her observations in a dynamic and interactive fashion, so it may be necessary for the therapists to ensure that the music is adequately "attuned" to the patient's dynamically unfolding experience and psychotherapeutic needs. Liking of the music may be an important primary pre-requisite for the individual to be able to relate personally and respond emotionally to the music. This liking may not only reflect the individual's aesthetic judgements, but could also refer to the suitability of the music styles to the conscious state induced by psychedelics. Needless to say, this area requires significant more research.

When the music is dissonant with the patient's emotional state, a change in the music may be required. This would include a better matching of the music's emotional and dynamic characteristics to the patient's present internal emotional state, on the assumption that this would help him or her experience these feelings more deeply, and that this experience would lead to meaningful therapeutic processing. For example, feelings of grief, can be matched with music that symbolises this *process* of grief. The capacity of music to not merely convey tonic emotional states, but also emotional dynamics (e.g. with nadirs, crescendo and breakthrough) may help develop a constructive and meaningful experience. To continue this example, the subsequent development of the resonant music is not merely reflecting a state of grief, but a dynamic *process* that can carry the engaged listener through a deeply felt emotional release, towards subsequent constructive resolution.

7.4.5 Implications for psychedelic therapy: Summary

The findings of this research suggest that psychedelics and music interact on subjective experience to provide a unique opportunity for experiential learning. A hypothetical framework was described in which psychedelics function to dissolve the usual psychological control mechanisms, thereby facilitating a substantial intensification of the subjective experience of the music. Music here has been suggested to have a two-fold function, one being directive/suggestive (activating), and the other being non-direct/non-suggestive (calming). The musical experience, in turn, has been argued to act therapeutically when the music is sufficiently attuned to (in resonance with) the patient's intrinsic dynamic feeling states, in order to facilitate a fuller emotional expression of these feeling states. When fully experientially *immersed* in the music, and when openly and interactively *engaged* with this experience, music can facilitate personally meaningful experiences (autobiographical experience and peak experiences), via which new self-concepts can be acquired that can form the basis for sustained positive therapeutic changes.

7.5 Study limitations and future directions

The research findings present several limitations and opportunities for future research (see paragraphs 3.4.2, 4.4.5, 5.4.3 and 6.4.6) First, despite the GEMS being designed and formulated to specifically assess music-evoked emotions, the experimental design of the studies reported in study 1 (Chapter 3) and study 2 (Chapter 4) did not allow us to separate drug-effects from music-effects on emotion. For example, LSD may have produced sensations of "transcendence" alone, without the music, and increased ratings of music-evoked transcendence under LSD and music-listening may therefore be influenced by this. Future studies are warranted that better enable a separation between music- and drug-conditions to deepen our understanding of their interactive effects on emotion. Secondly, although such design was implemented for the study assessment of LSD's and music's effects on mental imagery, reported in study 3 (Chapter 5), only a trend-level effect of music was observed for enhanced "complex" visual imagery. Mental imagery was however significantly enhanced by LSD alone. It may be that music influences a certain component of mental imagery, and as such, more specific measures may be needed to detect those changes, such as for example measures that not only assess vividness of the visual imagery, but also the content or the visual imagery. The absence of finding a significant music effect or a significant interaction-effect of music and LSD on visual mental imagery, may also be due a significant variance within the study population and the study population being small. This explanation is supported by the correlation-analyses in study 3 (Chapter 5), showing individuals with increased PHC→VC information flow reporting increased mental imagery, while other individuals reported decreased PHC→VC information and decreased mental imagery under LSD in response to music.

Using a similar line of reasoning, the study reported in study 2 (Chapter 4) showed a positive correlation between music-specific changes in brain-activity (i.e. to timbral complexity) and music-evoked emotion (wonder and transcendence). One may argue that if an effect on emotion was primarily due to LSD alone, a neurobiological measure highly specific to a feature within the music (i.e timbral complexity) would not be expected to correlate with changes in music-evoked emotion.

Finally, the qualitative findings discussed in study 4 (Chapter 6) provided insight into patient-experiences, but the lack of placebo condition emphasises the care needed in drawing strong inferences. The study should be valued for its exploratory nature, and its discussion, including the suggested possible therapeutic functions of music, must be viewed as speculative. The study provides directions for future studies where these hypotheses can be tested directly, and under placebo-controlled conditions. Examples of future studies that can test these hypotheses via better controlled experiments, are studies that assess the predictive value of liking of the music, resonance of the music, and openness to the music for subjective experience and therapy outcomes. Self-rating-scales can be implemented for the general experience of the playlist, or better, for specific genres of music. Such a study would have capacity to identify separate factors within the music-experience, and could help identify aspects of the music-experience (e.g. optimisation of music's resonance via an adaptive approach) may yield better therapy outcomes. Other important facets invite further investigation are the role of an individuals' music-listening history (individuals' usual music taste) in determining the music-experience under a psychedelic, and the relative contribution to music to the therapeutic experience and outcome compared to other factors in therapy sessions, such as for example interpersonal factors or the design of the physical environment in which the experience takes place. Furthermore, studies can aim to better understand the interactions between mind-set (mood and attitudes) and personality-traits (ex: trait absorption, openness, suggestively) with the subjective experience of music under psilocybin.

Research that focusses on identifying reliably indicators for positive (welcomed/supportive) and negative (unwelcomed/unsupportive) influences of music on the therapeutic processes during psychedelic therapy sessions, may be highly significant for the development of psychedelic therapy, and the tools used during psychedelic therapy. These could range from physiological measures, such as heart-rate, body movement, and breathing patterns, or more complex measures such as facial affect-coding, vocal-affect coding, and brain mechanisms (EEG-signatures), that could yield technologist that can assist therapists in on-the-fly adaptation of music-selection to maximise music's attunement to the individual's therapeutic needs, or inform playlist generation algorithms.

It must be emphasised that these studies were amongst the first to assess the combined effects of music and psychedelics on subjective experience and on brain function. The findings therefore naturally necessitate their replication in future independent studies. For example, the choice of music may have significantly influenced the present findings, and future studies that use different or a multitude of musical genres, may be utilised to control for this. Additionally, although the majority of individuals in the neuroimaging study and the clinical study reported a "liking" of the music, no measures were implemented to assess music taste or attitudes to music-listening beforehand, and these variables could have influenced the presented the results too.

7.6 Concluding remarks

The findings reported in this thesis support the hypothesis that the music-experience is intensified under psychedelics, and provide support for the widely-held view that this effect can be therapeutically utilised. Further research is warranted to better understand the brain mechanisms of psychedelics and music, and the therapeutic mechanisms of music in psychedelic therapy.

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Appendix:

Study-details for behavioural and clinical studies referenced in chapter 1.6.1 -1.6.6

Abbreviations: LSD; Lysergic Acid Diethylamide; DMT; Dimethyltryptamine, VLD; Very low dose, LD; Low dose, MD; Medium dose; HD; High dose, CBT; Cognitive-behavioural therapy, FTCD; Fagerström Test for Cigarette Dependence, TQD; Target Quit Date, 5D-ASC; 5-Dimensional Altered States of Consciousness Scale, 11D-ASC; 11-Dimensional Altered States of Consciousness, MEQ; Mystical Experience Questionnaire, ARCI; Addiction Research Center Inventory, SIP; Short Inventory of Problems, BAC; Breath Alcohol Concentration, SOCRATES 8A; The Stages of Change Readiness and Treatment Eagerness Scale, AASE; The Alcohol Abstinence Self-Efficacy Scale, PACS; The Penn Alcohol Craving Scale, POMS; The Profile of Mood States, NEO-PI-3; the NEO Personality Inventory 3, TLFB; Timeline Follow-back, QSU; Questionnaire on Smoking Urges, SASE; Smoking Abstinence Self-Efficacy Scale, HRS; Hallucinogen Rating Scale, SOCQ; States of Consciousness Questionnaire, SCID-IV; Structured Clinical Interview for DSM-IV, BPRS; Brief Psychiatric Rating Scale, YMRS; Young Mania Rating Scale, HAM-D; Hamilton Rating Scale for Depression, MADRS; Montgomery-Asberg Depression Rating Scale, GAF; Global Assessment of Functioning, QIDS; 16-item Quick Inventory of Depressive Symptoms, BDI; Beck Depression Inventory, STAI-T; Spielberger's State-Trait Anxiety Inventory [trait version], SHAPS; Snaith-Hamilton Pleasure Scale, fMRI; functional Magnetic Resonance Imaging, WSWS; Wisconsin Smoking Withdrawal Scale, EORTC-QLQ-30; European Cancer Quality of Life Questionnaire 30-item version 1.0, HADS; Hospital Anxiety and Depression Scale, GRID-HAMD; GRID-Hamilton Depression Rating Scale, HAM-A; Hamilton Anxiety Rating Scale, BSI; Brief Symptom Inventory, MQOL; McGill Quality of Life Questionnaire, LOT-R; Life Orientation Test-Revised, LAP-R; Life Attitude Profile-Revised, DEM; Demoralization Scale, HAI; Hopelessness Assessment and Illness, DAS; Death Anxiety Scale, DTS; Death Transcendence Scale, WHO-Bref; World Health Organization Quality of Life scale, brief version, FACIT-SWB; Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being, YBOCS; The Yale-Brown Obsessive Compulsive Scale, VAS; Visual Analogue Scale, FERT; Facial Emotion Recognition Task, MET1; Multifaceted Empathy Test, PLMT; Pattern/Line Meanings Task, ZKPQ; Zuckerman-Kuhlman Personality Questionnaire, FPI; Freiburg Personality Inventory, TAS; Tellegen Absorption Scale, PASI; Passive-Spontaneous Imagination, SCL-90-R; The Symptom Check-List-90-Revised, SVO; Social Value Orientation, MET2; Motivational Enhancement Therapy

Behavioural / questionnaire studies					
Study	**Drug**	**Dose**	**Route of admini-stration**	**Tasks/Questionnaires**	**Timing of task/questionnaire relative to drug-administration (prior, baseline or post)**
Vollenweider et al., 1998	Psilocybin	250 µg /kg	Oral	APZ-OAV DRT (Delayed Response Task)	Prior: unspecified Post: 80 min
Hasler et al., 2003	Psilocybin	VLD = 45 µg/kg LD = 115 µg/kg MD = 215 µg/kg HD = 315 µg/kg	Oral	5D-ASC AMRS Frankfurt Attention Inventory	unspecified
Carter et al., 2005	Psilocybin	215 µg/kg	Oral	Multiple Object Tracking CANTAB (spatial working memory)	Prior: unspecified Post: 120 min
				5D-ASC	180 min
Griffiths et al., 2006	Psilocybin	30mg/70kg	Oral	Monitor Rating Questionnaire	Prior: 10 min Post: 30 min, 60 min, 90 min, 120 min, 180 min, 240 min, 300 min and 360 min
				Hallucinogen Rating Scale APZ ARCI States of Consciousness Questionnaire Mysticism Questionnaire	Post: 7h
				PEQ Mysticism Scale	Post: 2 months

				Spiritual Transcendence Scale NEO PI-R PANAS-X	
Wittmann et al., 2007	Psilocybin	MD = 115 µg/kg HD = 250 µg/kg	Oral	Sensorimotor tasks	Prior: unspecified Post: 90 min
				AMRS	Baseline Post: 80 min and 280 min
				5D-ASC	Post: 110 min
				SSP (CANTAB)	Baseline Post: 100 min and 360 min
Wackermann et al., 2008	Psilocybin	VL= 12 µg/kg MD = 115 µg/kg HD = 250 µg/kg	Oral	Duration Reproduction Task AMRS	Prior: unspecified Post: 90 min and 240 min
				ASC	Not specified
Griffiths et al., 2008	Psilocybin	30mg/70kg	Oral	VAS	Post: 0.5 – 6 h
				HRS APZ Mysticism Scale Pahnke-Richards Mystical Experience Questionnaire	Post: 7 h
				NEO PI-R PANAS-X Quality of Life Inventory Measure of Actualisation Potential	Post: 2 months 14 months

				Mysticism Scale Spiritual Transcendence Scale Faith Maturity Scale FACIT-Sp-NI-12	
				PEQ	Post: 2 months
				Retrospective Questionnaire	Post: 14 months
Griffiths et al., 2011	Psilocybin	0, 5, 10, 20 and 30 mg/70 kg Ascending order in 1 month intervals	Oral	Hallucinogen Rating Scale APZ ARCI State of Consciousness Questionnaire Mysticism Scale (Experience-Specific)	Post: 7h
				Retrospective Questionnaire PEQ Mysticism Scale (Lifetime) DTS	Post: 1 month and 14 months
Carhart-Harris et al., 2011	Psilocybin	1.5 mg and 2 mg	IV	Post-drug ratings questionnaire	Post: 25 min
				5D-ASC	Post: 60-90 min
Maclean et al., 2011	Psilocybin	30mg/70kg 0, 5, 10, 20 and		NEO Personality Inventory	Baseline Post: 1 and 2 months

		30 mg/70 kg Ascending order in 1 month intervals		States of Consciousness Questionnaire	Post: 7 h
				Mysticism Scale	
				APZ	Unspecified
Quednow et al., 2012	Psilocybin	260 µg/kg	Oral	PPI (prepulse inhibition)	Post: 60 min
				Stroop Task	Post: 85 min
				5D-ASC	Post: 125 min
Kometer et al., 2012	Psilocybin	215 µg/kg	Oral	Facial Emotional Recognition Emotional Go/Nogo task EEG 5D-ASC PANAS STAI-S	Post: 130 min
				Self-report	Post: 360 min
Schmid et al., 2015	LSD	200 µg, 2.84 ± 6.13 µg/kg (mean and SEM; range, 2.04–3.85 µg)	Oral	5D-ASC VAS	Prior: 24 h Baseline Post: 0.5 h, 1 h, 1.5 h and 24 h
				AMRS ARCI	Prior: Unspecified Post: 3 h, 10 h and 24 h
Kuypers et al., 2016	Ayahuasca	Group 1 (mean and SD): 75.5 ± 11.1 mg DMT, 98.4 ± 14.4 mg harmine, 88.6 ± 13.0 mg	Oral	PLMT Picture Concept Task	Prior: 3 h Post: 1.5-2 h
				VAS	Post: After acute effects subsided (not specified)

		tetrahydroharmine, and 11.3 ± 1.7 mg harmaline Group 2 (mean and SD): 42.8 ± 14.9 mg DMT, 21.4 ± 7.5 mg harmine, 30.8 ± 10.8 mg tetrahydroharmine, and 4.6 ± 1.6 mg harmaline			
Dolder et al., 2016	LSD	100 and 200 μg	Oral	FERT MET_1	Post: 5 h (for 100 μg) and 7 h (for 200 μg)
				SVO	Post: 6 h (for 100 μg) and 8 h (for 200 μg)
				VAS AMRS	Repeatedly (not specified)
Family et al., 2016	LSD	40 and 80 mcg	IV	Picture-naming task	Post: 180–300 min
Preller et al., 2016	Psilocybin	215 μg /kg	oral	Cyberball Task	Post: during fMRI (not specified)

Clinical studies

Study	Drug	Dose (all oral)	Procedures	Duration of procedures	Tasks/Questionnaires	Timing of task/questionnaire relative to drug-administration (prior, baseline or post)
Moreno et al., 2006	Psilocybin	VLD: 25μg/kg LD: 100 μg/kg MD: 200 μg/kg HD: 300μg/kg	PAT for obsessive compulsive disorder	8h	YBOCS VAS	Baseline Post: 4h, 8h and 24h
Grob et al., 2011	Psilocybin	0.2mg/kg	PAT for end-of-life anxiety	8h	HRS	Post: 8h
					POMS	Prior: Day

					STAI 5D-ASC Brief Psychiatric Rating Scale	Post: ending of each session
					BDI POMS STAI	Post: One day, 2 weeks, and at monthly intervals for 6 months
Bogenschutz et al., 2012	Psilocybin	0.3 mg/kg 0.4 mg/kg	PAT for alcoholism Psychosocial intervention (MET_2)	4 sessions before 1st psilocybin session, 4 sessions between 1st and 2nd psilocybin session, and 4 sessions after 2nd psilocybin session	HRS 5D-ASC SOCQ MEQ SOCRATES 8A AASE PACS POMS Hood Mysticism Scale PEQ ASPIRES Spiritual Transcendence Scale Brief Multidimensional Measure of Religiousness/Spirituality NEO-PI-3 Schwartz Value Survey ARCI SIP	Post: 7h
					TLFB	Baseline: covering 12 week prior to enrollment
					BAC	Every session
Gasser et al., 2014	LSD	200 µg (experimental dose) and 20 µg (active placebo)	PAT for end-of-life anxiety	8h	SCID STAI-T EORTC-QLQ-30 SCL-90-R HADS	Baseline Post: 1 week, 2-month, 12-month
			Drug-free psychotherapy	60-90 min	SOCQ	After each experimental session

			Follow-up evaluation	2 months after second experimental session		
Johnson et al., 2014	Psilocybin	20mg/70kg 30mg/70kg	Preparation meetings: CBT based on “Quit For life” programme	90 min - Weekly for 4 weeks prior to TQD	TLFB FTCD	Baseline Post: Every week 2-15 and 6-month
			Integration meetings	1h - Day after psilocybin session	QSU SASE WSWS	Baseline Post: 6 weeks,, Week 8-15 and 6-months
			Support meetings	45 min - Weekly after TQD for 10 weeks	Visual Effects Questionnaire	Baseline Post: 6-months
			Support meetings PAT for smoking cessation	45 min - Weekly after TQD for 10 weeks 8h	Post-session Headache Interview	Post: One day
			Support meetings PAT for smoking cessation TQD	45 min - Weekly after TQD for 10 weeks 8h At 5th week	Mysticism Scale	Baseline Post: 1-week, 2 weeks and 3 weeks
					SOCQ	Post: 7h
					PEQ	Post: 1 week after every session
					TQD	Baseline
					TQD QSU SASE	Baseline Post: weekly and 6-months
Garcia-Romeu et al., 2014	Psilocybin	20mg/kg 30mg/kg	TQD Medical interview Laboratory tests Assessment of tolerability	At 5th week Not specified	TQD QSU SASE HRS	Baseline Post: 7h, weekly, 6-months,
			TQD Medical interview Laboratory tests Assessment of tolerability	At 5th week Not specified Check-in and physiolo	Mysticism Scale SOCQ	Post: At end of each session
					Ratings of Personal Meaning,	Post: 15 weeks

			Non-directive approach	gical recordings at 30, 60, 120, 180, 240, 300, and 360 min post dose	Spiritual Significance, and Well-being	
					BPRS YMRS HAM-D MADRS	Prior: 10 minutes Post: 40min, 80 min, 140 min, 180 min; 1 day, 7 days, 14 days, 21 days
					QIDS BDI STAI-T SHAPS	Baseline Post: 1 day and 3 days after high dose
Osorio et al., 2015	Ayauasca	120-200 ml (2.2 ml/kg) Ayahuasca 0.8 mg/ml DMT 0.21 mg/mL harmine	Non-directive approach Experimental sessions	Check-in and physiological recordings at 30, 60, 120, 180, 240, 300, and 360 min post dose 8h	11D-ASC	Post: 6-7h
Carhart-Harris et al., 2016	Psilocybin	Low: 10 mg (2 x 5 mg) High: 25 mg (5 x 5 mg)	Non-directive approach Experimental sessions Drug-free psychotherapy sessions	Check-in and physiological recordings at 30, 60, 120, 180, 240, 300, and 360 min post dose 8h	HAM-D MADRS GAF	Post: 1 day (after high dose)
					QIDS	Post: 2, 3, and 5 weeks
					SCID STAI-T EORTC-QLQ-30 SCL-90-R HADS	Baseline Post: 1 week, 2-months, and 12-months (after high dose)
					SOCQ	After each experimental session

				60-90 min		
			Follow-up evaluation	2 months after second experimental session	SOCQ GRID-HAM-D-17 HAM-A with SIGH-A BDI HADS STAI POMS Total Mood Disturbance Subscale BSI MQOL LOT-R LAP-R Death Acceptance DTS Purpose in Life Test LAP-R	Baseline Post: After each experimental session, 5 weeks, and 6-months
Gasser et al., 2014	LSD	200 µg (experimental dose) and 20 µg (active placebo)	Meetings with session monitors (non-directive and supportive)	Day after each session (mean 1.2 h), on two or more occasions between first and second session (mean 2.7 occasions for a mean total of 3.4h), and on two or more occasions between second session and 6-month follow-up	SOCQ GRID-HAM-D-17 HAM-A with SIGH-A BDI HADS STAI POMS Total Mood Disturbance Subscale BSI MQOL LOT-R LAP-R Death Acceptance DTS Purpose in Life Test LAP-R HADS BDI STAI	Baseline Post: After each experimental session, 5 weeks, 6-months Prior: 1 day Post: 1 day after, 1-2 weeks after, 6 weeks after, 7 weeks after dose 1 (corresponding to 1 day prior to dose 2) 1 day after, 6 weeks after, and 26 weeks after dose 2

			Assessments	6 weeks post dose 1, 6 weeks post dose 2 6-month follow-up		
Griffiths et al., 2016	Psilocybin	Low: 1mg/70kg High: 22mg/70kg	Assessments	6 weeks post dose 1, 6 weeks post dose 2 6-month follow-up	DEM HAI DAS DTS WHO-Bref FACIT-SWB PEQ	2 weeks post dose 1, 26 weeks post dose 2
Ross et al., 2016	Psilocybin	0.3mg/kg	Oral	Assessments	6 weeks post dose 1, 6 weeks post dose 2 6-month follow-up	HADS BDI STAI
						DEM HAI DAS DTS WHO-Bref FACIT-SWB PEQ
						MEQ

Appendix: The music playlist

The music playlist used in the depression trial is displayed below. Please note that following this playlist, an updated version of this playlist has been developed. Also note that the playlist used did not merely list the songs in the structure suggested below, but included a mixing of volume, fade-ins, fade-outs, etc. Other playlists are developed that employ different music styles and target different therapy objectives. For access to the latest version of this playlist and other works, visit www.mendelkaelen.com

Music playlist (v1.2.) for psychedelic therapy sessions for depression with psilocybin

Time	Track
00:00:00	Stars of the Lid - Dungtitles (In A Major)
00:05:57	Stars of the Lid - Articulate Silences Part 1
00:11:20	Stars of the Lid - Articulate Silences Part 2
00:16:58	Stars of the Lid - Evil that never arrived
00:22:03	Harold Budd & John Fox - Sunlit Silhouettes
00:25:05	Harold Budd & John Fox - A Delicate Romance
00:32:36	Brain Eno & Harold Budd - Against the Sky
00:37:29	Brain Eno & Harold Budd - Lost in the Humming Air
00:41:43	Robert Rich & Lisa Moskow - Bija
00:52:24	Robert Rich – Sagrada Familia
00:56:15	Robert Rich – The spiral steps
	Silence (3 minutes)
01:08:34	Henry Gorecki - Lento - Sostenuto Tranquillo Ma Cantabile
01:33:44	Maria Bayo & Sinfonica De Tenerife - Bailero
01:39:25	David Darling – Prayer for compassion
01:43:36	David Darling – Stones start spinning
01:47:53	Carlos Cipa – The Whole Truth

01:53:25	Greg Haines – 183 Times
02:02:36	Harold Budd & John Fox – Coming into focus
	Silence (30 seconds)
02:08:06	Ludovico Einaudi - The Journey
02:10:43	Arvo Part – Da Pacem Domine
02:16:28	Max Richter – The Young Mariner
02:20:39	Max Richter – Diner and the ship of dreams
02:26:07	Henryk Gorecki - Lento e Largo Tranquillissimo
02:35:41	Greg Haines – Azure
	Silence (20 seconds)
02:50:12	Otto A. Totland - Open
02:52:42	Otto A. Totland - Steps
02:54:34	Federico Albanese - Disclosed
	Silence (50 seconds)
03:01:21	Dead Can Dance - Devorzhum
03:07:30	Robert Rich - Amrita (Water of Life)
03:13:56	Ólafur Arnalds & Alice Sara Ott - Verses
03:17:54	Ólafur Arnalds & Alice Sara Ott - Piano Sonata No.3 Largo
03:26:58	Ólafur Arnalds & Alice Sara Ott - Nocturne in C Sharp Minor
03:31:23	David Darling – Beautiful Life
03:33:30	David Darling – When we Forgive
03:37:35	Enya - sumiregusa
03:42:20	Jon Hassel, Ry Cooder & Ronu majumdar - Bay of Bengal
03:47:08	Jon Hassel, Ry Cooder & Ronu majumdar - River song
	Silence (25 seconds)
04:12:55	Anugama - Shamanic dream
	Silence (20 seconds)

04:24:26	Arvo part - Spiegel Im Spiegel
04:35:12	Nest - Stilness
04:40:49	Arve Henriksen - Glacier descent
04:48:17	Arve Henriksen - Opening Image
04:52:33	Arve Henriksen - Hambopolskavalsen
04:57:54	Daniel Namkhay - Um Bolero Galíctico
	Silence (15 seconds)
05:04:05	Dead Can Dance - Nierika
	Silence (15 seconds)
05:09:49	Brian McBride – Toil Theme Part 1,2& 3
05:17:31	Nils Frahm - Ambre
05:21:19	Nils Frahm - Tristana
	Silence (2.5 minutes)
05:42:44	Mozart - Ave Verum Corpus
05:46:46	Mercedes Sosa - Gracias a la Vida
05:51:17	Ladysmith Black Mambazo - King of Kings
05:55:33	Buffy saint Mary - Up where we belong
06:00:10	Olafur Arnalds & Alice Sara Ott - Letters of a traveler
06:04:22	Stars of the Lid - Don't Bother They're Here