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Psilocybin and Music: Proposal to Study the Effects of Music on Efficacy of Psilocybin-Assisted Therapy for Treatment-Resistant Depression

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by

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Abstract

This paper proposes an experiment to investigate the efficacy of psilocybin-assisted therapy for treating treatment-resistant depression (TRD) and assess the modulating effects of music on therapeutic outcomes. Previous studies have consistently incorporated music into psilocybin-assisted therapy for TRD but have not empirically isolated its effects. This research aims to fill this gap by introducing a controlled variable of music to explore its impact on therapy efficacy. I hypothesize that listening to the music playlist created by Johns Hopkins University during therapy sessions will significantly enhance therapeutic outcomes compared to a control group listening to ambient sounds. Participants, adults diagnosed with TRD, will be randomly assigned to either music group or non-music group and will undergo two psilocybin-assisted therapy sessions. Depression severity will be quantitatively measured using the Quick Inventory of Depressive Symptomatology (QIDS), Beck Depression Inventory (BDI), and Snaith-Hamilton Pleasure Scale (SHAPS) at various time points to evaluate immediate and enduring changes in symptoms. The findings are expected to provide insights into the synergistic potential of music and psilocybin and contribute to the advancement of therapeutic protocols in psilocybin-assisted therapy for TRD.

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Brief Overview of the History of Psychedelic Drugs

In the 20th century, the Swiss chemist Albert Hofmann was working with ergot, which is a fungus affecting rye, and by accident, discovered the psychoactive properties of lysergic acid diethylamide, or LSD. After being affected by the drug through accidental skin absorption, Hofmann started experimenting with the drug on himself, and dedicated a lot of his time to investigating the hallucinogenic properties of LSD, believing that the drug could be useful in psychiatric contexts for treating schizophrenia and other types of illnesses. In his book (Hofmann, 2009) Hofmann writes about his first intended "trip" and the famous bicycle ride home. He writes about the distortions and changes that he experienced, both visually, and, as he calls it, changes in his inner being. He describes feelings of ego dissolution, sensations of dying, and out-of-body experiences. As he writes in his book after his experience with the drug, he knew that it would be of use in pharmacology, neurology, and psychiatry, but what he did not expect was the coming popularity of LSD as a recreational drug. Hofmann writes that even though he expected the drug to be of interest to some outside of the scientific world - like performers, painters, and writers - he did not expect the drug to become one of the most popular recreational substances of the era. In 1966, the United States Congress passed the Drug Abuse Control Amendment, banning the individual manufacturing of LSD and other hallucinogens of the same type (Encyclopedia.com, 2023). 1970 marked the date when almost all the government-sanctioned human research on psychedelic drugs was stopped, as President Nixon introduced the Controlled Substances Act (Beckley Foundation, 2017). In the early 2000s, after a pause of a few decades, the research began to slowly grow in momentum, with multiple promising studies using psilocybin being conducted. Psychedelic research has been growing since.

Pre-20th Century Era:

Even though the 20th century and Albert Hofmann's experimentation marked an important point for the Western interest in psychedelic substances, these substances have been used for much longer. The earliest evidence of possible ritual psychedelic use is found in representations in cave rock art, with the oldest example being a mural depicting *Psilocybe mairei*, a psychoactive mushroom native to the region, in a cave in Tassili-N-Ajjer region of the Sahara, in Algeria (Kennedy, 2014, p. 116). It depicts what became to be known as the "Mushroom Man", a figure with a head of a bee and with mushrooms sprouting out of its body. Another possible evidence comes from a prehistoric "Selva Pascuala" mural in Spain, which contains fungoid figures that the researchers believe to be *Psilocybe hispanica*, a species of psychedelic mushroom containing psilocybin and known to be grown in the area (Akers et al., 2011). The dried tops of the Peyote cactus, or *Lophophora williamsii*, found in Shumla Cave No. 5 on the Rio Grande, Texas, and the identified mescaline in them, suggests that North Americans knew about the properties of peyote 5700 years ago (El-Seedi et al., 2005). For further evidence for early psychedelic use, see (Buxton, 2014) and (Miller et al., 2019).

Figure 1:

The "Mushroom Man"

Note: Depiction of the "Mushroom Man," a figure with a head of a bee and with mushrooms sprouting out of its body. It is believed that the mushroom is Psilocybe mairei, a psychoactive mushroom native to the region where the painting was found, in a cave in Tassili-N-Ajjer region of the Sahara, in Algeria. From Kennedy, p. 116 (2014).

What are Psychedelics, and What is Psilocybin?

Substances like psilocybin, LSD, Mescaline, and 3,4-Methylenedioxy methamphetamine (MDMA) have been referred to by many different names (Hart et al., 2014). Because of their ability to change the subjective experience of reality and induce hallucinations in its user - a state that could be referred to as psychotic - such substances have been referred to as psychotomimetic drugs. This term, however, has a negative connotation, which could lead to biased and non-scientific opinions about these substances. Other terms such as entheogen and entactogen have also been used, with entheogens referring to the substances that induce spiritual or religious experiences (like mushrooms containing psilocybin), and entactogens (which literally means "to produce a touching within") referring to the substances that enhance feelings of empathy. This paper uses the word "psychedelics" to refer to, what has been referred to as the "classic psychedelics" - ones that can produce the effects without much acute physiological toxicity, like LSD, psilocybin, or Mescaline (Hart et al., 2014). This paper focuses specifically on psilocybin, an active ingredient present in a variety of "magic" mushrooms, including *Psilocybe mexicana, Psilocybe Cubensis*, and others, that binds to 5-HT2A serotonin receptors in the brain (Hart et al., 2014). The mushrooms, like a lot of other psychedelics, have a long history of religious and ceremonial use (Hart et al., 2014).

The Subjective Experience of Taking Psilocybin

A study conducted in 2016 examined the effects of psilocybin-assisted therapy on anxiety and depression in patients with life-threatening cancer diagnoses. A single moderate dose of psilocybin (0.3mg/kg), in conjunction with psychotherapy, was found to produce rapid and lasting (up to 8 months) reduction in anxiety and depression (Ross et al., 2016). A qualitative study conducted in 2018 studied the subjective experience of four of these patients, providing a great deal of insight into the nature of psychedelic experiences of this

kind (Malone et al., 2018). Before giving a detailed account of these experiences, it is necessary to address the question: is learning about the nature of the subjective experience of taking psilocybin important?

Learning about the subjective experience of taking psilocybin is important for a few reasons. A study that found that high-dose psilocybin intake (22-30 mg/70 kg) produced large and long-lasting decreases in self-rated and clinician-rated measures of anxiety and depression, and increases in quality of life, life meaning, and optimism, also found a significant association between mystical-type experience and enduring therapeutic outcomes (Griffiths et al., 2016). This was the case even when the intensity of the experience was controlled for, suggesting that it is mystical experience per se, not the intensity necessarily, that leads to positive outcomes. All of this suggests that studying the nature of subjective experience, and understanding which aspects of it are important and useful for the user, is important, because it could yield a better understanding of the mechanisms of the therapeutic process. Later, in another paper, Yaden and Griffiths developed the argument further, suggesting that subjective experience is a crucial component in creating enduring therapeutic effects (Yaden & Griffiths, 2020). If the subjective nature of the experience indeed holds such weight, it needs to be talked about.

Another interesting fact to have in mind when reading these subjective experiences is how different these people's backgrounds are in terms of age and religion. This is important, because it suggests that very different types of people could benefit from the experience - one need not be a follower of a specific ideology or religion. Something else to bear in mind is how similar some of the emerging themes of their experiences are, even while a large portion of the content itself is very different, suggesting that even though the experiences might differ a lot, they might also, at the same time, share as much.

Victor, one of the participants of the study (Malone et al., 2018), and a male in his 20s, renounced his Jewish faith after being diagnosed with non-Hodgkin's lymphoma during his high school. He felt that god had failed him, and he was faced with the truth of vulnerability of his own body. Even though he was in remission, he had severe anxiety and occasional panic attacks, and was diagnosed with adjustment disorder with anxiety, chronic. Victor told the interviewers that during the experience, he felt as if there was a spiritual guide present, and as the emotions that he experienced became too overwhelming, the spiritual guide was coming in, interestingly, through music. After experiences like witnessing a whole life cycle of his, including his birth and death, and feeling "tremendously painful" helplessness after witnessing his family attend his own funeral, the spiritual guide would "blast me out of that experience into a new setting." Victor describes how he felt that he did not have a body, that he was just an entity, a soul, and how he was looking for a body to enter. He said that the only body that he could pick was his own, and described this experience as the process of resolving his issues with the illness that affects his body. He describes how he saw everything that has happened to his body throughout his life, including food, sex, exercise, and tells the interviewers about how he chose his own body, and accepted it. The "spiritual guide" that was present in his experience told him that if he is loving and kind to others, he might be able to meet god one day, and he had other experiences that were full of love of meeting his loved ones who've passed away. According to the data, his anxiety decreased, while his feeling of purpose in life, spirituality and death transcendence increased. What is interesting about the experience is that it seems like, at some points, it was largely uncomfortable and painful; facing death and seeing one's own funeral do not seem to be what one would call a "positive" experience, but still, the experience proved to be incredibly useful, suggesting that one of the reasons why these experiences could be potent is the fact that they make one confront very uncomfortable ideas and fears, such as death.

Tom, a 50-year-old Christian male with Chronic Myeloid Leukemia, met the diagnostic criteria for adjustment disorder with anxiety, chronic. Tom noted that the music from the study's pre-selected playlist played a huge role in his experience, describing the experience of hearing the music not just as hearing, but as playing, as if his "entire body was the musical instrument" for every sound which was coming through his head. He described seeing the music as three-dimensional shapes of different colors and talks about the sense of all-knowingness that he experienced - the sense of knowing that there is nothing to fear after death, nothing at all. He also describes feeling an overwhelming feeling of love, and an urge to tell everyone about it, and to tell everyone that nothing really matters but love. As he said, the experience gave him a greater appreciation for his life and helped him lose the fear of death. It is important to note that his anxiety and depression, hopelessness, demoralization, and death anxiety decreased only moderately, and that he described being underwhelmed and disappointed by the experience in some way. He stated that even though the experience was intense, and even though he liked it, it was not life changing. Even though the experience did not prove to be as useful to Tom, the subjective nature of it is still noteworthy and warrants a close look. The theme of death and the fear of death is present again, and so is the theme of love and appreciation of life.

Chrissy, a female in her 50s, an atheist, diagnosed with stage 4 breast cancer, with a diagnosis of generalized anxiety disorder, described feeling strong sensations of unity and connection with the world and others. At some points in her experience, she heard a voice in her head, a voice that was not her own, saying "we are here all together". She experienced themes of life and death multiple times during her experience, in different contexts. At one point, she was seeing beautiful stone faces that would come to dust, then come back up, then come to dust again, and so on and so on. At another point, she saw a Ferris wheel, which for her resembled a cycle of life and death, and how one comes out of another. She experienced a

sensation of being at peace with death, thinking that she would surrender when the time comes. Interestingly, while feeling open and accepting of death, she felt like her experience helped her reach the decision of choosing to live. This part of Chrissy's experience bears resemblance to Victor's previously mentioned experience, when he described that he was an "entity" looking for a body, after which he came to choose his own body, and saw this as a resolution of his issues with the illness that affects him. The experiences share the theme of acceptance and autonomy - Chrissy decided to live, while Victor chose his own body. Chrissy's anxiety, depression, hopelessness, death anxiety, and demoralization decreased, and a feeling of purpose in life, death transcendence, and spirituality increased. She talked of the experience as something that has "brought my beliefs to life, made them real, something tangible and true - it made my beliefs more than something to think about, really something to lean on and look forward to." This is an interesting statement, given that Chrissy described herself as an atheist. This demonstrates that having an affiliation with religion is not an important factor for having a fruitful spiritual experience. In the end, as Chrissy described, her having cancer stopped being as important, because at the end, everyone will face the same death.

For Brenda, a female in her 60s with stage one colon cancer and a second-time diagnosis of cancer, a self-identified atheist, who was diagnosed with adjustment disorder with anxiety, chronic, the psychedelic experience was her first one. The most important theme in her experience, as she described it, was the sense of interconnectedness and unity, the feeling that she is everything, and that everything is her. She described the feeling, or the belief, as wonderful, and said that she continues to believe in what she felt during the experience. She also described experiencing her own death two times. She emerged from these experiences with having less fear of death and saw it as a beautiful component of life. Again, the theme of acceptance of the inevitable emerges. At some point, she describes going

into a black area, which she interpreted as death, and feeling that it was wonderful. She thought of death as something beautiful. Another theme that surfaced in her experience was the childhood memory of sexual assault, and she thought about the psychedelic experience as a catalyst for beginning the healing process. She reported that for her, everything has changed after the experience, and that she feels more content about her place in the world. She also reported that even though she is not at all religious, she felt like a new kind of spirituality opened up in her, and she became interested in developing a relationship with the new spiritual side of herself. Because she valued the experience a lot, the researchers report, she started to seek out opportunities to re-experience it, started meditating, and felt a new and strong, "real" connection with Buddhism. This is similar to Chrissy's remark, that the experience brought her beliefs to life, that it made them real, tangible, and true.

These experiences are as different in their content as they are similar. Victor witnessed his own funeral, Chrissy was looking at stone faces that were going through the cycle of coming to dust and reemerging, Brenda was thinking about her childhood trauma, and Tom felt like he was "playing" the music that he was hearing. On the other hand, all these experiences share the theme of reappreciation of life, rethinking of death and the fear of it, feelings of love, acceptance of the given and the inevitable, and a general sense of appreciation.

The reason for including this detailed report of subjective experiences of taking psilocybin is to demonstrate to the reader what do these experiences look like. Taking psilocybin strongly differs from the experience of taking other standard medicines, and these reports provide further context and a deeper understanding of what it is that the paper is discussing. Another reason for including these subjective reports is to show that the experiences can be influenced a lot by the setting that the participants are in – and this is

important to keep in mind while reading this paper, because the experiment that it proposes relies on changing the experience by introducing a variable of music.

Psilocybin-Assisted Therapy for Depression and Anxiety - Current State of Literature

This section provides an overview of the current literature and evidence of using psilocybin-assisted therapy as a treatment for depression and anxiety. Even though the focus of this study is depression, it makes sense to look at both depression and anxiety when reviewing the literature, because the two are highly comorbid and frequently share some symptoms (Kalin, 2020). At the same time, they share a lot of neural mechanisms, such as a deficit in the circuitry that is normally associated with adaptation to emotional conflict - dampening of amygdala activity and an increase in ventral cingulate activity during an emotional conflict task (Etkin & Schatzberg, 2011). It is important to note, however, that Etkin & Schatzberg (2011) also found differences in neural activity during the task, such as activation of the anterior lateral prefrontal cortex, which was present only in depressed participants, and behavioral differences, suggesting that even though the disorders share a lot, they also differ.

Wheeler & Dyer (2020) conducted a systematic review of psychedelic-assisted therapy for mental health, where they cite multiple studies providing evidence for the efficacy of the treatment. The following section includes the studies that are cited in this article.

The first study using psilocybin for anxiety and depression associated with life-threatening cancer diagnoses found decreases in anxiety levels for up to 6 months after the session (Grob et al., 2011). Another study conducted 5 years later found that a single-dose administration of psilocybin in conjunction with psychotherapy resulted in acute and sustained antidepressant effects for up to 6.5 months after the session (Ross et al., 2016). In another study, 2 sessions of psilocybin-assisted psychotherapy lead to antidepressant effects for up to 3 months after the second session (Carhart-Harris et al., 2016). A study using fMRI

found an association between psilocybin-assisted therapy and increased amygdala response to fearful stimuli, and stronger reactions were associated with better treatment outcomes (Roseman et al., 2018). Interestingly, previous research has shown that SSRIs attenuate amygdala responses (Ma, 2015, as cited in Roseman et al., 2018), which is the opposite of what psilocybin was found to be doing in this study (Roseman et al., 2018), suggesting that the mechanisms underlying the treatment are different when comparing SSRIs and psilocybin. It is possible that SSRIs work through mitigating negative emotions, while psilocybin works through helping patients to confront these emotions and work through them. This is consistent with the aforementioned subjective reports of taking psilocybin that describe how the patients were going through a lot of difficulties and emotional challenges throughout their experiences. Another study found that after psilocybin-assisted therapy, individuals with treatment resistant depression (TRD) had faster emotional face processing times compared to baseline, and reaction times were positively correlated with decreased anhedonia, which is a key component of depression (Stroud et al., 2017).

Psilocybin and Music

Studies on psilocybin and music go hand in hand, it is almost impossible to find a study that involves administering psilocybin and does not involve music. A lot of studies are using already created and established music playlists, such as the playlist created by John Hopkins University (see appendix E). As the John Hopkins University website describes, the playlist, available on Spotify, is divided into different segments: background music, which plays when the participant arrives for their session; music that plays as the drug starts to take effect, at which point they lie down and wear eye shades and headphones; the high; the peak; the post-peak; and the 'welcome back' music. The music used in each of the sections has been deliberately chosen to accompany a particular part of the psychedelic journey. For example, Bill Richards, the creator of the playlist, says that he finds that Samuel Barber's song "Adagio

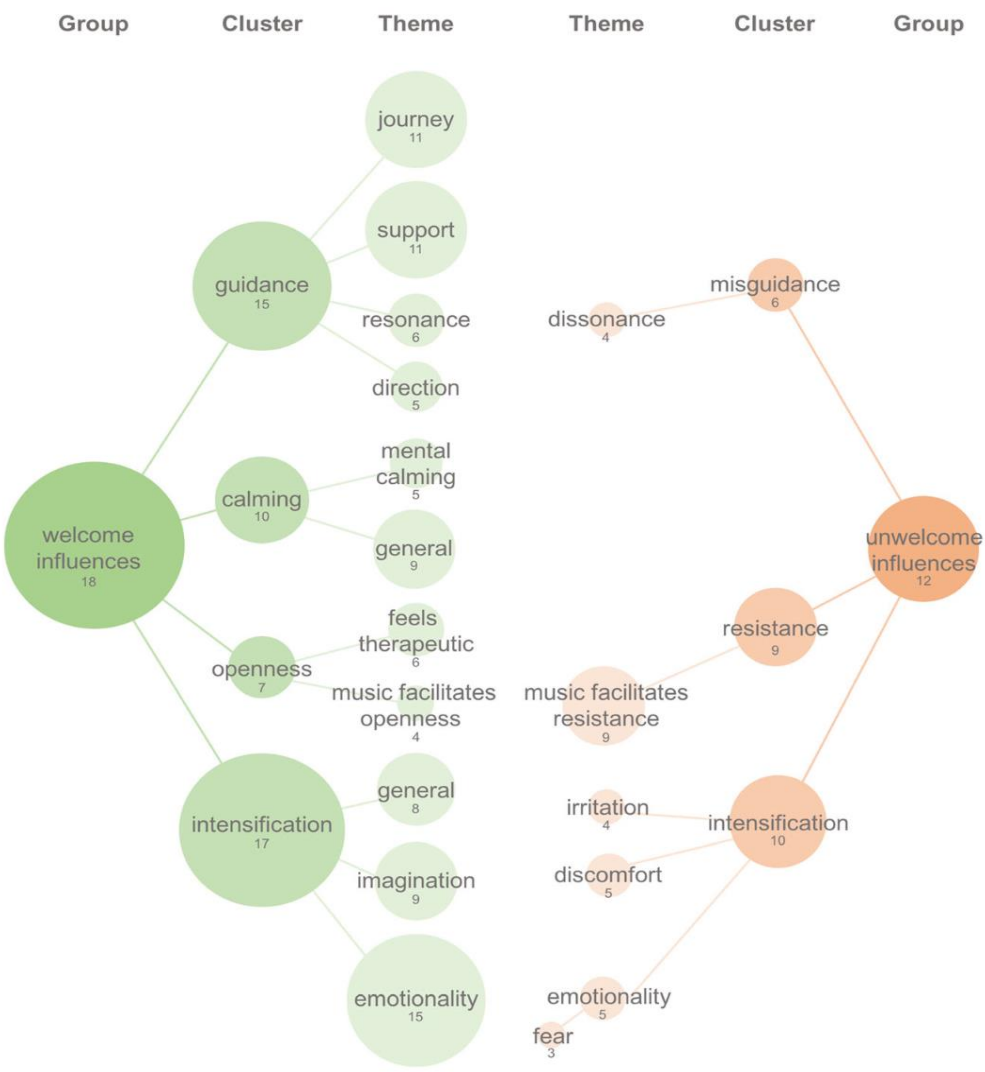
for Strings" is a good accompaniment for when the participants approach the peak, when the effects of psilocybin become more intense. He notes how the music develops chromatically, goes up, reaches the climax, and then comes back down. Additionally, he states that the music helps prevent participants from returning to normal consciousness too soon, and that it can provide structure in case of getting anxious (Shapiro, 2021).

According to subjective reports, music plays an important role in psilocybin-assisted therapy for treatment resistant depression (Kaelen et al., 2018). Music intensified both emotional experiences and mental imagery by enhancing or changing emotions and by evoking vivid, complex imagery related to it, and it had both welcome and unwelcome influences on the experiences of the patients. Welcome influences included the evocation of meaningful emotions and mental imagery, a sense of guidance, a sense of openness, and a sense of calm. Many felt that the challenging experiences evoked by music were an important part of the process, with reports stating that the music helped listeners to connect with and face their inner conflicts. Unwanted influences included unpleasant emotions, a sense of misguidance and a feeling of resistance caused by it. Nearly half of the patients expressed resistance to the music-evoked experience, including not liking or not wanting the subjective effects created by the music. This resistance, of course, is in contrast with the sense of guidance that the others experienced. Half of the patients reported that the music intensified emotions they did not want to feel, such as fearfulness, sadness, or fear, and reported that the music often created a sense of discomfort, including unpleasant or uncomfortable experiences. About 40% described being irritated because of the music. Interestingly, some reported that the music blocked their feelings. What is very interesting is that reduction in depression one week post therapy was significantly predicted by the music experience variables of liking, resonance, and openness, and not by the drug intensity, indicating that the

music played a more crucial role than the drug intensity in improving depressive symptoms (see Figure 2 for visual demonstration).

Figure 2

Welcome and Unwelcome Influences of Music



Note: Welcome influences are in green on the left, and unwelcome influences are in red on the right. The numbers below the group, cluster, or theme name refer to the total number of patients who were related to it. The size of the circle is proportional to the percentage of patients referring to the group, cluster, or theme. Figure from Kaelen et al. (2018).

According to these subjective reports, music seems to be playing a very important role. However, it is very hard to say how much of the positive therapeutic outcomes are related to it without testing the causal link directly. Up to date, there have been no studies comparing the conditions of psilocybin-assisted therapy for treating treatment resistant depression (TDR) in conjunction with music versus without music. The questions regarding music's role in psilocybin-assisted therapy are endless, but to utilize the power of music properly, first it is necessary to establish a causal link between music and positive therapeutic outcomes. That will be the goal of the experiment that this paper proposes to conduct.

What do we Known About Music?

Earliest Evidence of Music Tradition

Music, from the modern perspective, seems almost indistinguishable from human experience. Music surrounds us everywhere and is seen as a ubiquitous aspect of human society. To date, there have been no reports of a modern society that does not have music in some shape or form. When exactly did humans invent musical instruments is a contested topic, but current earliest evidence of bone and ivory flutes indicates that more than 35000 years ago, on the territory of modern southwestern Germany, musical tradition was present (Conard et al., 2009). What is interesting, however, is that even though understanding music is usually treated as an ability that comes after the ability to understand language, some researchers argue that humans' ability to understand music predates language and is actually an essential element of language acquisition (Brandt et al., 2012). Either way, music seems to be integral to human experience. At this point, lots of interesting and important questions pop up: What could be the function of music in human society? How does music affect individuals? What does scientific research about music tell us? But before answering these very important questions, it is important to talk about the most basic question: What constitutes music at all?

What is Music?

Seems like everyone knows what music is, but even though seemingly obvious, it is a very tricky thing to define. Montagu (2017) gives one of the simplest definitions, by saying that music is a "sound that conveys emotion". Which emotion is conveyed, he says, does not matter – as long as it is used intentionally to convey a certain emotion, it is music. He adds that music also involves an intentional change in pitch, which can be defined as highness or lowness of the soundwave frequency, and rhythm, which can be thought of as ordered recurrent alteration of sounds. Of course, this definition can be challenged from a lot of different angles. First of all, speech also seems to fit this definition: it is also a sound, and it also conveys an emotion. Additionally, human speech involves changes in pitch as well. Think about someone's voice when they ask a question very politely, versus when they demand something very aggressively. And rhythm can also by manipulated in speech by elongating or shortening words in a sentence. Brandt et al.'s (2012) definition of music might satisfy some more than that of Montagu's, which they say is a "creative play with sound; it arises when sound meets human imagination."

It is important to keep in mind that even though it seems like everyone knows what music is, it is something that could be defined in many ways, and what for some constitutes music, for others might not.

Evolutionary Origins of Music

There are various theories about the evolution of music. In this paper, three of the most prevalent viewpoints of music will be discussed: sexual selection, social bonding, and music as a byproduct of evolutionary processes.

Sexual Selection. The idea that music evolved as a means of promoting an individual's genetic quality and increasing their fitness through reproductive success is widely accepted in both evolutionary psychology and popular science literature. This theory aligns

with common human intuitions derived from folk psychology, as many musical works across cultures often center around themes of love, betrayal, and intimate relationships (Mehr et al. 2019, as cited in Kalinowski et al, 2021).

In one study, the researchers analyzed the prevalence of topics related to what they call "reproductive categories" in the lyrics of the 174 songs that made it into the *Billboard* Top Ten for Pop, R&B, and Country genre charts during 2009 (Hobbs and Gallup, 2011). The reproductive categories included any lyrics that were related to genitalia or other body parts in a sexual way, references to dating, hand-holding and other courtship displays, references to short-term relationships and "hook ups", and any language directly related to sexual activity. According to the researcher's calculations, approximately 92% of the total of 174 songs that were in the Top 10 in the year 2009 contained reproductive messages, with the content analysis revealing 18 consistent reproductive themes that, as the researchers state, "read like topics taken from an outline for a course in evolutionary psychology." Analyses revealed that the songs that made it into the list included significantly more reproductive references and messages than the songs that did not manage to make it into the Top Ten.

According to Darwin, "musicality" is sexually selected for and therefore is important in mate choice (Darwin, 1871). It has been proposed that music can serve the similar function, cognitively speaking, as does the peacock's tail – the ability to produce it and being proficient at it is translated to reproductive success and attracts partners (Miller, 2000, 2001 as cited in Kalinowski et al, 2021). However, despite the popularity of this notion in popular culture, it is supported by very little evidence (Kalinowski et al, 2021).

The Social Bonding Hypothesis. Music is universally woven into the social fabric of human life, serving as the central element of major life events across cultures, from weddings to funerals, regardless of the religiousness or secularity of a society. The widespread use of music underscores its deep-rooted connection to essential human social processes (Loersch

and Arbuckle, 2013). Music's presence in both special and everyday human interactions demonstrates its profound social nature, suggesting its evolutionary role in strengthening social bonds within groups (Kalinowski, 2021).

In one study, four-year-old children were divided into 2 conditions (Kirschner & Tomasello, 2010). In the musical condition, pairs of children danced around a pond while singing and playing percussion instruments, while in the non-musical condition, they did exactly the same except all the musical features were omitted. In subsequent tests of cooperation and prosocial behavior, the children who were in the music group displayed more prosocial and cooperative behavior than those who were in the non-music group.

Singing has been shown to mediate fast social bonding (Weinstein et al., 2016). Pearce et al. (2015) conducted a study to explore whether bonding arises out of properties that are intrinsic to music itself, or whether any other type of social engagement can have a similar effect. The researchers underscore how previous research that has studied the topic has focused on one-time singing sessions instead of exploring social bonding over longer period of time. Pearce et al. (2015) followed adult educational classes of singing and non-singing (such as creative writing or crafts) over a period of seven months. Participants reported their feelings of closeness to their group and their emotional connection at three different timepoints: one month, three month, and seven months in. The researchers found that by timepoint three, which was seven months into the class, both singers and non-singers felt equally connected to each other. Singers, however, demonstrated a significantly greater increase in closeness at timepoint one, one month in. This provides evidence for the idea that the understanding and use of music in humans might have evolved for social bonding and cohesion.

Music as a Byproduct of Evolution. The theory that music, instead of being a direct evolutionary adaptation, is simply a byproduct of human evolution, is a significant viewpoint

in the debate about the origins of music in human society. This perspective is sometimes referred to as the "auditory cheesecake" hypothesis, a phrase famously coined by cognitive psychologist Steven Pinker (Pinker, 1997). This hypothesis stipulates that even though music is pleasurable, it serves no biological function and is not fundamentally necessary for human survival or reproduction. What this analogy implies is that just as cheesecake capitalizes on our appetites for sugar and fat, music leverages humans' sound processing capabilities that evolved for reasons that were adaptive, like language, emotional communication, and environmental awareness, and is simply a coincidental byproduct of these qualities.

These types of byproducts, in the context of biology, have been referred to as "spandrels," which is defined as a phenotypic characteristic of an organism that is a byproduct of the evolution of other characteristics, instead of being a direct result of adaptive selection. Interestingly, it is a term that is borrowed from architecture, where spandrel is a term referring to the space between an arch and a rectangular enclosure around it. It exists only because of the need for an arch and the rectangular enclosure around it to exist, meaning that it is just a coincidental, unnecessary byproduct of what is necessary.

The view that music is also just a spandrel has been extensively challenged in scientific literature. Research on amusia, which is a neurological condition that makes it hard to distinguish between musical pitches and affects tonal memory as well, shows that the human brain has specialized areas that are particularly responsive to music (Peretz & Zatorre, 2005). The existence of such specialized neural mechanisms indicates that music may have been important enough in human evolution to exert selective pressure on the development of the brain.

Application of Music in Therapy

There are many ways in which music can be utilized in therapy. According to American Music Therapy Association, music therapy generally refers to the clinical and

evidence-based practice of using musical interventions within a therapeutic relationship to achieve individual therapeutic goals. It can involve listening to live or recorded music, moving to music, creating and producing music, or reproducing it on different instruments.

Music has been shown to have positive effects on depression, one study even finding that a group of depressed patients undergoing music therapy, which consisted of listening to about 50 minutes of classical music a day for 8 weeks, had more improvements in their depression than the group undergoing conductive-behavioral psychotherapy (Castillo-Pérez et al., 2010). This might be due to the release of several neuropeptides, including dopamine, that play part in producing the pleasurable sensations that diminish depressive states and enhance positive emotions (Burgdoft & panksepp, 2006, as cited in Castillo-Pérez et al., 2010).

A meta-analysis of 55 randomized controlled trials found that music therapy is associated with significant reductions in depressive symptoms (Tang, Q. Et al., 2020). Another study using fMRI has also found that intense pleasure in response to music can lead to dopamine release in the striatal system, illustrating that listening to music can have effects that are similar to those evoked by other types of rewarding stimuli (Salimpoor et al. 2011). Given that depression is often accompanied by a lack of interest in pleasurable stimuli, the music's effect on the brain regions involved in reward, and its ability to provoke pleasurable responses, can be very useful in counteracting depression (Blood & Zatorre, 2001).

To connect it back to the psilocybin-assisted therapy, if music can be effective as a stand-alone treatment, it seems reasonable to assume that it plays an important role in psilocybin-assisted therapy as well.

Rationale

It is evident that while there is a growing body of research highlighting the potential of psilocybin-assisted therapy for treating treatment-resistant depression, the specific role of music within this therapeutic context remains underexplored. Current research lacks direct

experimental studies that isolate the effect of music in psilocybin-assisted therapy. Thus, there is a compelling rationale for conducting a study specifically designed to test the hypothesis that playing music during psilocybin-assisted therapy sessions can improve therapeutic outcomes in patients with treatment-resistant depression. Such a study would not only fill a critical gap in psychedelic research, but also, potentially, guide research towards investigating more effective, nuanced therapeutic protocols and approaches that integrate music as a central component in the treatment of depression.

The Description of the Study That the Paper Proposes to Replicate and Extend

To study the role of music in efficacy of psilocybin-assisted therapy, I will replicate and extend the study conducted by Carhart-Harris et al. (2016). But first, I will provide an overview of their study.

It was an open-label feasibility study on psilocybin with psychological support for treatment-resistant depression. It involved 12 participants who received two oral doses of psilocybin (10 mg and 25 mg) seven days apart, accompanied by psychological support before, during, and after administration.

The primary outcome measured was the mean change in self-reported depressive symptoms, which was measured in a lot of different ways: 16-item Quick Inventory of Depressive Symptomatology (QIDS), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI-T), Snaith-Hamilton Pleasure Scale (SHAPS), Hamilton Depression Rating Scale (HAM-D), Montgomery-Åsberg Depression Rating Scale (MADRS), and Global Assessment of Functioning (GAF), all were taken at different points in time. Below are the brief explanations of what each measurement does, and the specific details of when each measure was taken.

The Quick Inventory of Depressive Symptomatology (QIDS) is a 16 item self-report measure of depression. The Beck Depression Inventory is a 21 item self-report measure of

depression. The State-Trait Anxiety Inventory – Trait (STAI-T) is a 40 item self-scored measure of day-to-day anxiety. The Snaith-Hamilton Pleasure Scale (SHAPS) is a 14-item self-scored measurement for assessing anhedonia. The Hamilton Depression Rating Scale (HAM-D) is a 21-item measure designed to rate the severity of depression in patients, and it needs to be administered by a health care professional. The Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item measure used to assess the severity of depression of an individual as seen and assessed from the perspective of a health care professional. Lastly, Global Assessment of Functioning (GAF) is a health professional's subjective assessment of an individual's social, occupational, and psychological functioning.

HAM-D, MADRS, and GAF are measures that need to be taken by a psychiatrist, which requires additional resources: participants need to come in into the research facility, and a psychiatrist needs to be present. Because of this, these measurements were only taken as baseline measures, and once more, 1 week after the high-dose session. All the other measures were ones that need to be self-administered, making it possible to conduct them remotely.

The 16-item Quick Inventory of Depressive Symptomatology (QIDS) was taken at each time period: the baseline, 1, 2, 3, and 5 weeks, and 3 months after the high-dose session.

Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI-T), and Snaith-Hamilton Pleasure Scale (SHAPS), were taken as baseline measures, 1 week after the high-dose session, and 3 months after the session.

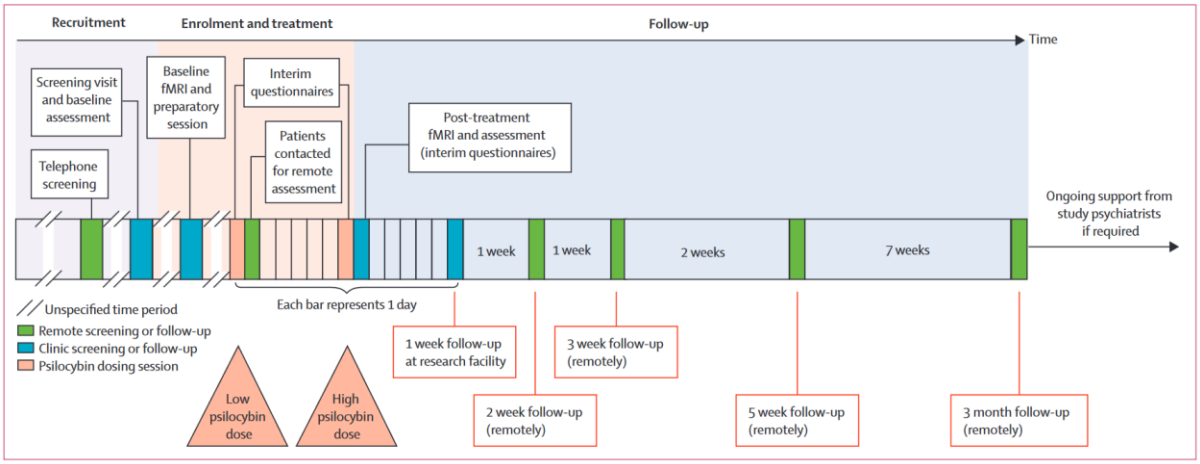
The acute psychedelic effects of psilocybin were noticeable within 30–60 minutes after administration, peaking between 2–3 hours, and diminishing to negligible levels by 6 hours post-dosing. Importantly, psilocybin was well-tolerated by all participants, with no serious or unexpected adverse events reported. Notable transient adverse reactions included

anxiety at the onset of the drug's effects, confusion or thought disorder in nine patients, mild nausea in four patients, and headache in four patients.

Crucially, the study reported significant reductions in depressive symptoms, demonstrating a significant improvement one week after the treatment, which was sustained three months later. The study observed significant and lasting improvements in anxiety and anhedonia among participants. These results provide preliminary evidence supporting the safety and efficacy of psilocybin as a treatment for depression, underscoring the need for further research through more rigorous trials to fully explore psilocybin's therapeutic potential. My goal is to provide a proposal to extend this study by adding a variable of music, and seeing if it influences the therapeutic outcome. I predict that listening to the playlist created by John Hopkins University enhances therapeutic efficacy of psilocybin-assisted therapy in treating TRD.

Figure 3

Schedule of the Study Intervention conducted by Carhart-Harris et al. (2016).



Note: This is the schedule of the study intervention that Carhart-Harris et al. (2016) conduct. The study that I propose follows a similar outline. FMRI measurement, however, can be completely ignored, as it is irrelevant to this study. Figure from Carhart-Harris et al. (2016).

Method

Participants & Recruitment

Participants will be recruited by sending the information about the study to general practitioners registered in New York State, who will then pass on the information, including contact information, to their patients. Willing candidates will then themselves initiate contact with the research team, will be sent additional information about the study, and a telephone screening will be arranged, in which the lead psychiatrist will obtain additional information about the patients, including demographics, medical conditions, and all the other excluding criteria. Each patient's general practitioner will be asked to provide a written diagnosis of the patient's treatment-resistant major depressive disorder and their mental health background history. All participants will provide written informed consent. Judging from the previous literature, and considering convenience, a total of 30 participants will be needed, 15 in each group.

Inclusion & Exclusion Criteria

The inclusion criteria will be major depression of a moderate to extreme degree, which will be defined as a score of 21 or more on Beck Depression Inventory (BDI), and a history of no improvement in symptoms despite administration of two courses of antidepressant treatment of different pharmacological classes lasting a minimum of 6 weeks and located within the current depressive episode. Exclusion criteria will include a history of being diagnosed with psychotic disorders, a history of immediate family members being diagnosed with psychotic disorders, any other medical condition which might render a candidate unsuitable for the study, history of suicide attempts, history of mania, blood or needle phobia, being pregnant at the time of screening or anytime afterwards, and current drug dependence.

Procedures

First meeting

Participants will be scheduled to come to a research facility (a hospital) for screening. Each participant will come individually. The process of screening will include written informed consent, an evaluation of the candidate's health background, a psychiatric interview (Mini-International Neuropsychiatric Interview), and assessment of depression severity by Beck Depression Inventory (BDI), Quick Inventory of Depressive Symptoms [QIDS], and the Snaith-Hamilton Pleasure Scale [SHAPS]. In addition to these measures, patients will undergo physical health examination, consisting of routine blood tests, blood pressure, heart rate, and electrocardiogram (by using the equipment that the medical team sees fit).

First Meeting Continues – Preparatory Session

Eligible participants will be assigned to music group or non-music group based on their order of coming into a hospital. The first participant will be assigned to music group, the second to non-music group, the third to music group, and so on. After the screening, participants will have a preparatory session with their psychiatrists, in which participants will be able to talk extensively about their history, depression, and thoughts on possible origins of their condition. Psilocybin's effects will be discussed to give the participants a general sense of what kind of an experience to expect, and a simulation of some of the aspects of the dosing session will be held. In case of having a session with the member of music group, the simulation will include wearing eyeshades and listening to music, while in case of non-music group, the simulation will include wearing eyeshades and listening nothing, which will amount to normal sounds of the room and the facility. The session will last 2-4 hours and will include breaks and lunch. After the preparatory session, the date of the first and second session will be scheduled, with the window of exactly one week between the sessions.

Table 1

Timeline of the Preparatory Meeting

Time	Event
9am	Participant arrives
9-9:30am	Informed consent
9:30-10:15am	Health assessment (routine blood tests, blood pressure, heart rate, ECG)
10:15-11:30am	BDI, QIDS, SHAPS
11:30am-1:00pm	MINI, open discussion and preparation for drug session
1:00pm	Participant returns home

The First Session – Low Dose

On any given day, only one patient will be dosed. They will arrive at a research facility at 9:00am, give a urine sample and perform a breathalyzer test. The urine sample will be tested on drugs of abuse, such as cannabinoids, opiates, benzodiazepines, and amphetamines, and the breathalyzer test will provide information about alcohol use. If any of these tests turn out to be positive, the participant will be excluded.

Participants will be assessed on BDI, QIDS, and SHAPS measurements to make sure that there is no substantial difference from the measures taken at baseline. Afterwards, patients will be led to the intervention room, and be invited to lay down or sit on a reclinable bed. In the case of the music group, the music will start playing. To accommodate participants' comfort, they will be given a choice between earphones or speakers. In the case of the non-music group, normal sounds of the room and the facility will be present, such as the sound of air conditioning, people moving around the facility, etc. Two psychiatrists will be seated near the bed, and patients will be uninterruptedly supervised throughout the session.

The dosing will occur at 10:30am, with every session strictly adhering to the same schedule. During the first session, the participants will receive the low dose of 10mgs of psilocybin (orally). Five minutes before dosing, the measures of heart rate and blood pressure will be taken. The same measurements will be taken throughout the session, 30, 60, 120, 180, 240, 300, and 360 minutes after receiving the dose.

The approach that the psychiatrists will take throughout the session will be supportive, but non-directive, meaning that the patients will be allowed to experience the entirety of their journey without additional guidance. Every time that the measurements of heart rate and blood pressure are taken, psychiatrists will check in with the participants to make sure that they feel well. The so called "trip killers", or tranquilizing medications that dampen the effects of psilocybin, will be present and administered if necessary. The necessity will be determined by the psychiatrists' judgment – if the psychiatrists decide that participants are undergoing too much discomfort, are in continuous pain for more than 15 minutes, and are asking for help, they will be given the tranquilizers. Transport to and from the research facility will be prearranged, and a friend or a close relative will accompany the participants. If participants express the willingness to stay in a hotel for the night, they will be accommodated in a nearby facility.

Table 2

Timeline of the Psilocybin-Assisted Therapy Session

Time	Event
9:00am	Participant arrives
9:00-9:30am	Urine test, breathalyzer, BDI, QIDS, SHAPS
9:30-10:30am	Participant prepared (bathroom, water) and relaxed

10:30am	Administration of psilocybin
10:30am-4:30pm	Acute drug experience
4:30-5:30pm	Thorough debriefing
5:30pm+	Participant returns home

One Day After the Low Dose Session

One day after the low-dose session, participants will be contacted to make sure they do not experience any adverse effects. No measurements will be taken at this point.

The Second Session – High Dose

During the second session, the participants will receive a high dose of 25mgs (orally). The procedure will be exactly the same as with the low dose.

One Day After the High Dose Session

One day after the high-dose experience, participants will go back to the research facility, complete BDI, QIDS, and SHAPS measures, and be invited by their psychiatrists to talk about the session and discuss the experience.

Subsequent Follow Ups (after 1, 2, 3, and 5 weeks, and 3 months)

After 1 week of the initial high-dose session participants will complete the assessments remotely (BDI, QIDS, and SHAPS) and email the results to the psychiatrist. In weeks 2, 3, and 5, only QIDS will be assessed, and this will be done remotely as well. The reason for only completing QIDS at these points of time is not to overburden the participants. In the final follow up, 3 months after the high-dose session, participants will complete all the measurements: QIDS, BDI, and SHAPS, and send the results to the psychiatrist, thus, finalizing their involvement.

Statistical Measures

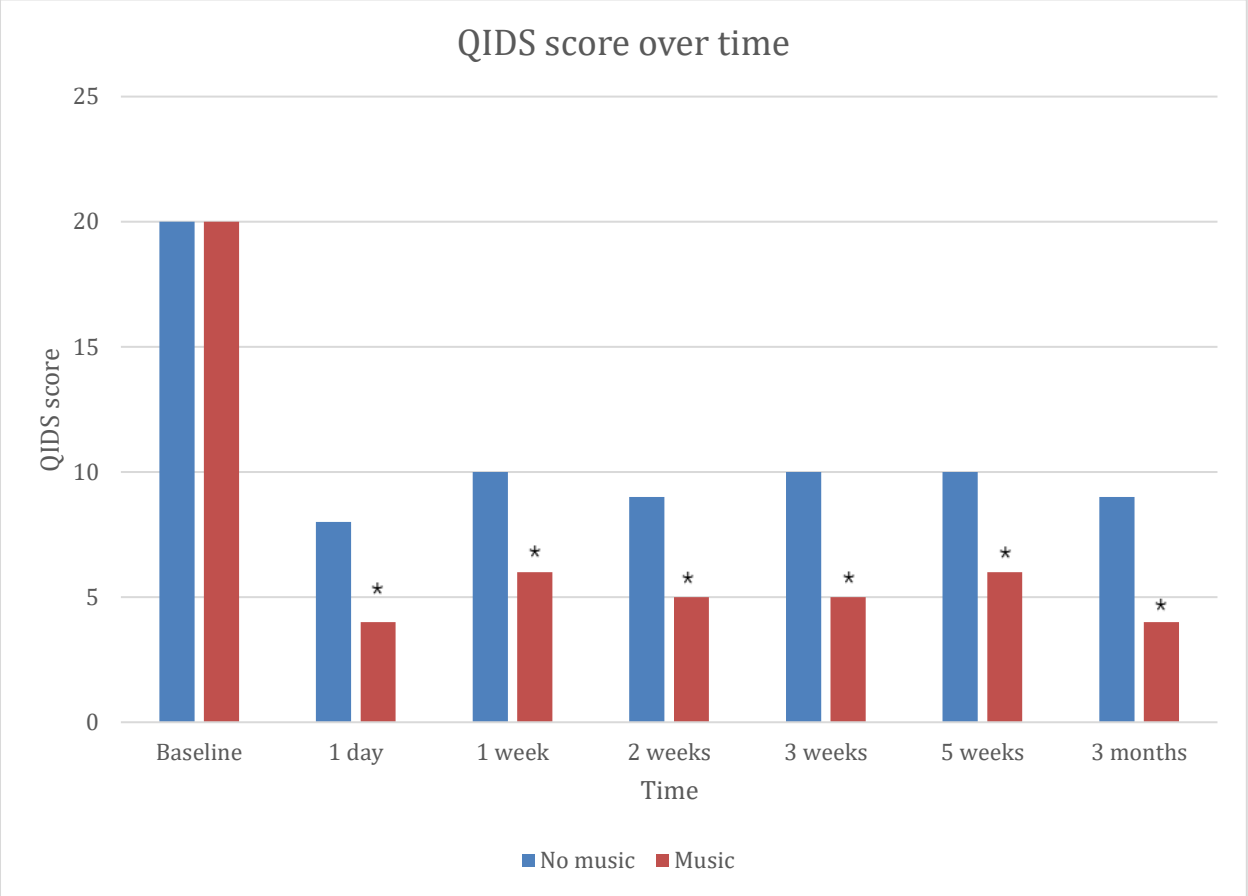
A mixed-design 2 (treatment) x 6 (time) analysis of variance (ANOVA) will be conducted to examine the effects of music and time on the efficacy of psilocybin-assisted therapy for treating treatment-resistant depression, with an alpha of .05. This statistical test will attempt to detect a difference between music and non-music groups from baseline to six different points in time.

Expected Results

Following the psilocybin-assisted therapy, both groups are expected to have significantly lower scores on BDI, QIDS, and SHAPS than their baseline, and the effects are expected to be sustained over the span of three months. The music group, however, is expected to have significantly more improvement, in every follow-up measure, than the non-music group.

Figure 4

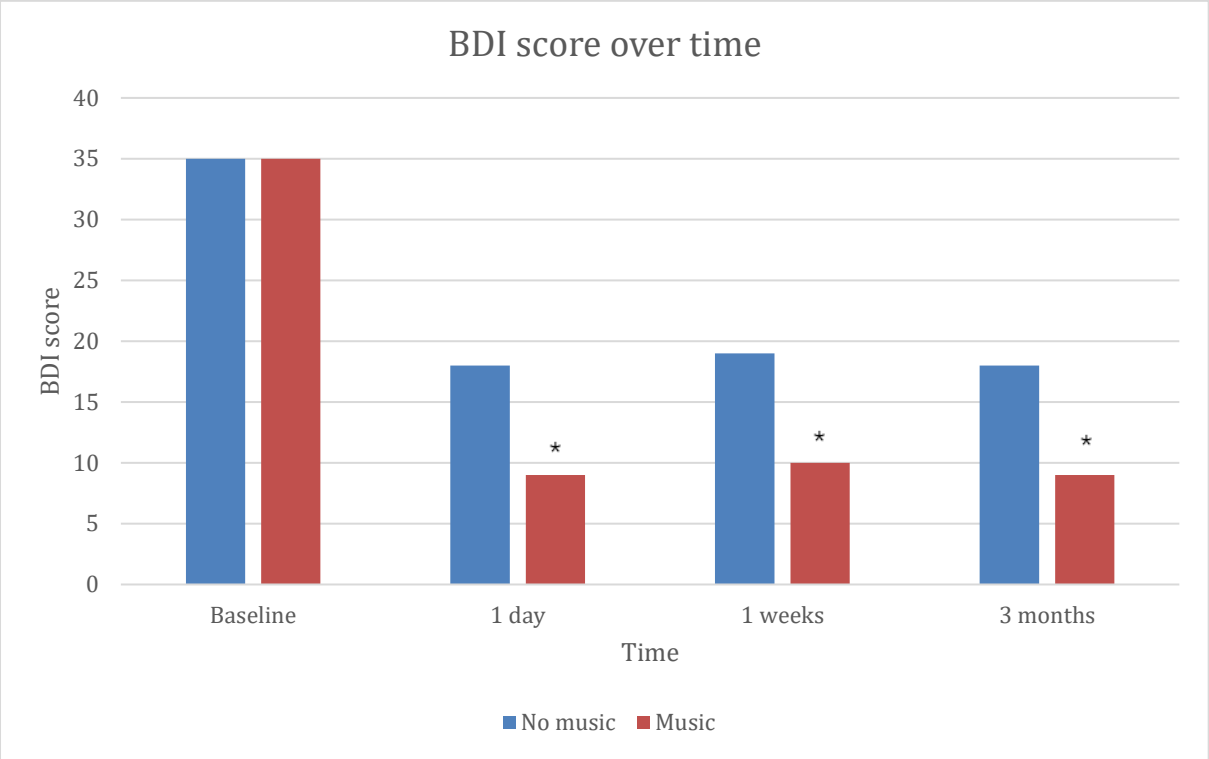
QIDS score over time



Note: The QIDS score of each group at baseline (before the psilocybin-assisted therapy) and at six different points of time after the high dose session. No music group is in blue, music group is in red. The difference between the groups is significant at each timepoint apart from the baseline. * = $p < 0.05$

Figure 5:

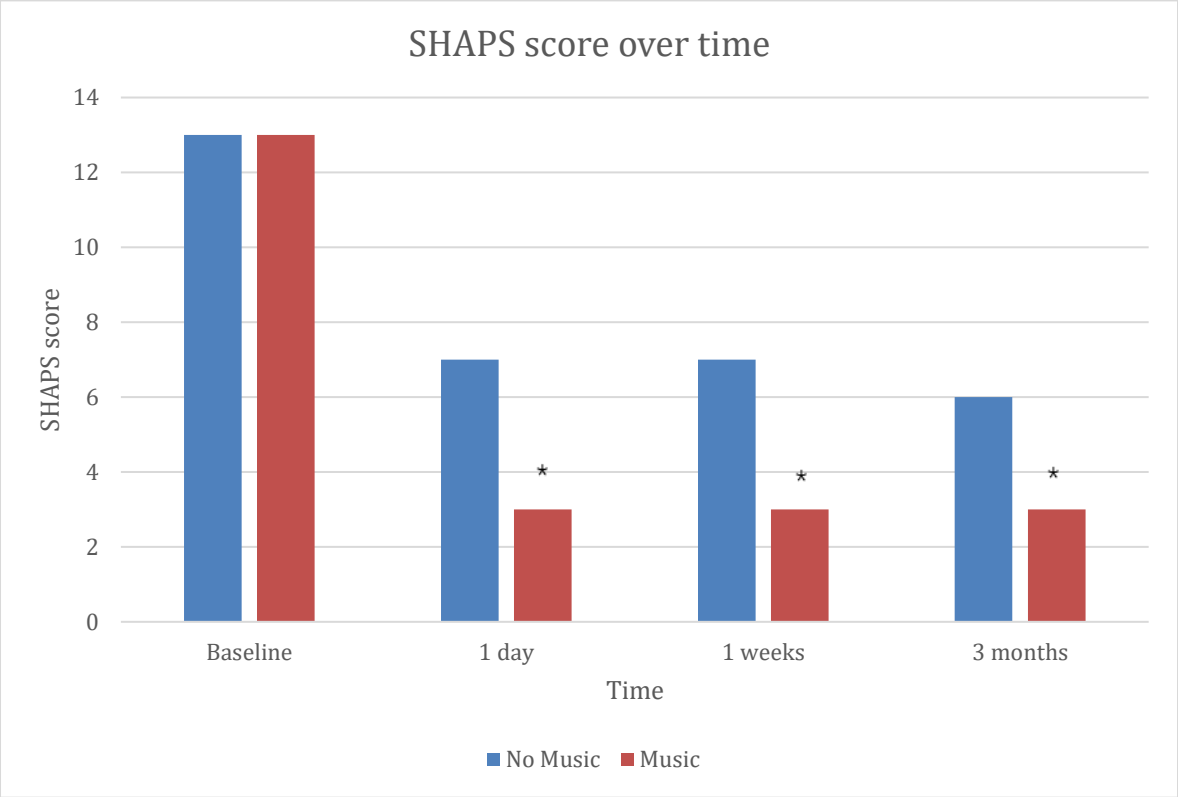
BDI Score Over Time



Note: The BDI score of each group at baseline and at three different points of time after the high dose session. No music group is in blue, music group is in red. The difference between the groups is significant at each timepoint apart from the baseline. * = $p < 0.05$

Figure 6

SHAPS Score Over Time



Note: The SHAPS score of each group at baseline and at three different time-points after the psilocybin-assisted therapy session. No music group is in blue, music group is in red. The difference between the groups is significant at each timepoint apart from the baseline. * = $p < 0.05$

Discussion

The current study aims to replicate the findings of the previous study (Carhart-Harris et al, 2016) by demonstrating significant reductions in depression scores for both groups, further supporting the efficacy of psilocybin-assisted therapy for treatment-resistant depression. Moreover, this study extends the scope of previous research by examining the influence of music on therapeutic outcomes. It is hypothesized that participants who listen to music during their therapy sessions will exhibit a greater reduction in depressive symptoms compared to those listening to ambient sounds. This would suggest that there is something about music that makes the therapy more effective. Even though music's efficacy and

usefulness in psychedelic research seems to be accepted as common sense, this study would be the first to empirically support the idea that music enhances therapeutic outcomes of psilocybin-assisted therapy for treatment-resistant depression.

The next logical step would be to ask what it is exactly about music that induces this effect. There are several possibilities. It could be that the emotional and mental states that music induces increase the efficacy of psilocybin-assisted therapy. Future studies could manipulate the variable of music in various ways to see what types of music are more useful for eliciting a strong therapeutic response in patients. The research could focus on studying the effects of different musical genres on the psilocybin-assisted therapy for different mental disorders. Could it be that one genre aids the therapy for one disorder, but disrupts the therapeutic effect for another one? An interesting question to explore indeed. Future studies could also focus on determining if different genres affect people in different ways, and if different people benefit from different types of music. This could lead to developing ways of tailoring music to individual patients. The researchers could also empirically test if particular types of music are more beneficial at different stages of psilocybin experience.

Rigorous empirical examination of music's effect on psilocybin-assisted therapy could provide scientific basis for manipulating music in ways that maximize its potential and therapeutic power. This could lead to developing more sophisticated and nuanced approaches to utilizing music, by tailoring it to specific stages of therapy, disorders, and people.

Limitations

First and foremost, this is an open-label design study, and the fact that the researchers and participants know that participants are receiving psilocybin could affect the outcomes. Additionally, having an active control condition would be useful in understanding if placebo effect plays a role in the therapeutic outcome.

Another limitation is the study's potential lack of generalizability. Participants are being recruited by providing general mental health practitioners of New York State with the information about the study. The fact that the participants are only recruited from New York State is a limitation, because the New York State population might not be representative of the whole U.S.A population.

Another possible limitation is the choice of music. Because the participants might have different preferences for music, using one and the same playlist for everyone could lead to different experiences, and if liking and disliking music influences the therapeutic outcome of the therapy, it could be hard to make generalized conclusions about the efficacy of music based on the data. In other words, more specific and detailed testing of different types of music for different types of people might be necessary to make a more generalized statement about music's usefulness.

Another possible consideration is the fact that the participants in the non-music group are exposed to regular sounds of a research facility, which could be very different from other types of sounds. It could be the case, for example, that the sounds of nature have a yet different effect. This study compares music to regular sounds of research facilities, while there are many other types of sounds that music could be compared to. If indeed this study shows that the music group has better outcomes than the non-music group, it would be reasonable to ask if other types of ambient sounds affect the outcomes in a different way.

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Appendix A

Informed Consent Form

TITLE OF STUDY

Psilocybin and Music: A proposal to study the effects of music on efficacy of psilocybin-assisted therapy for treatment-resistant depression.

PRINCIPAL INVESTIGATOR

Giorgi Gzirishvili
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PURPOSE OF STUDY

You are being asked to take part in a research study. You will undergo psilocybin-assisted therapy twice, first you will take a small dose and after one week you will take a large dose. Psilocybin is a classic psychedelic substance commonly found in certain types of mushrooms. The purpose of this study is to see if psilocybin-assisted therapy is useful for treating treatment-resistant depression.

STUDY PROCEDURES

You will undergo psilocybin-assisted therapy twice, first you will take a small dose and after 1 week you will take a large dose. Before the experience, and many times after, you will be asked to respond to a series of measures, sometimes by coming into the research facility, and at other times by doing it at home and sending your results to researchers by email. During your experience, you will always be accompanied by a therapist to provide guidance if needed.

RISKS

Given the type of experience that taking psilocybin usually is, there is a chance at experiencing major discomfort and distress. It is normal to feel distress during the experience, yet it might be very uncomfortable. It might involve feeling extremely anxious, fearful, and nervous. Additionally, there is a small chance of psychosis or having lasting changes in perception. During your experience gets so intense that you are no longer willing to go through it, you can ask your therapist to give you medication that will calm you down and reduce the intensity of the experience.

You may decline to answer any or all questions and you may terminate your involvement at any time if you choose.

BENEFITS

Psilocybin has the potential to help those with treatment-resistant depression. Therefore, there is a chance that you will directly benefit from participating in this study. In addition to direct benefits to you, you will help advance scientific research in the field, which will help in improving treatment options and helping more people.

COMPENSATION

All participants will be paid $20 for every in-person session, and $15 dollars for every time they need to take measures and send them to the researchers.

CONFIDENTIALITY

Every effort will be made by the researchers to preserve your confidentiality including the following:

- Assigning code names/numbers for participants that will be used on all research notes and documents.
- Keeping notes, interview transcriptions, and any other identifying participant information in a locked file cabinet in the personal possession of the researcher.

Participant data will be kept confidential except in cases where the researcher is legally obligated to report specific incidents. These incidents include, but may not be limited to, incidents of abuse and suicide risk.

VOLUNTARY PARTICIPATION

Your participation in this study is voluntary. It is up to you to decide whether or not to take part in this study. If you decide to take part in this study, you will have to sign this consent form. After you sign the consent form, you are still free to withdraw at any time and without giving a reason. Withdrawing from this study will not affect the relationship you have, if any, with the researcher. If you withdraw from the study before data collection is completed, your data will be returned to you or destroyed.

CONSENT

I have read and I understand the provided information and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without cost. I understand that I will be given a copy of this consent form. I voluntarily agree to take part in this study.

Participant's signature _____ Date _____

Investigator's signature _____ Date _____

Appendix B

Debrief Form

Study title:

Psilocybin and Music: A proposal to study the effects of music on efficacy of psilocybin-assisted therapy for treatment-resistant depression.

Principal Investigator:

Giorgi Gzirishvili

Purpose of the study:

The purpose of this study is to investigate the role of music in psilocybin-assisted therapy for treatment-resistant depression. This is done by comparing two groups of participants, those who listen to music during psilocybin-assisted therapy and those who do not.

Deception:

You were not informed about the fact that there are two groups, one that listens to music and one that does not. This was done to make sure that the results of the study are not affected by your expectations and thoughts about music's presence/absence.

Contact:

If you have any questions regarding this study, please do not hesitate to ask now or contact the principal investigator Giorgi Gzirishvili, email: gg9036@bard.edu. You can also contact the Institutional Review Board, email: irb@bard.edu.

Appendix C

Budget

Psilocybin: One gram of psilocybin costs around $7000 dollars. Each participant will take 35mgs in total, and there are 30 participants, which is a total of 1050 milligrams. This means that about $7350 dollars are needed for the psilocybin itself.

Participant compensation: $20 for every in-person session, $15 dollars for every online follow-up. There are 4 in-person sessions and 5 online follow-ups, which means that for each participant's compensation, a total of $155 dollars is necessary. Given that there are 30 participants, a total of $4650 is needed.

Research personal compensation:

Two psychiatrists will be paid $100/h. Each preparatory session will take 4 hours, thus with 30 participants it will take a total of 120 hours, which means that $1200 is needed for the preparatory sessions. The psilocybin sessions each take around 8 hours, each participant participates in 2 sessions, thus 16 hours for each participant. Both psychiatrists are present at all times, so 32 hours total for both psychiatrists with each participant; 32*30 = 960 hours, which means $9600 dollars for psilocybin-assisted sessions. The practitioner who gathers and analyzes data will be paid $50/h, so counting about 3 hours for each participant, 90 hours total, $4500 for the practitioner.

Taking everything into account, a total of about $27,300 is necessary for this study.

Appendix D:

IRB proposal form

- **Section 1**

Please enter the following information about yourself:

- Today's date: 04/20/2024
- Name: Giorgi Gzirishvili
- Email: gg9036@bard.edu
- Your Academic Program/Department/Office: Psychology
- Your status (faculty, staff, graduate or undergraduate student): Undergraduate Student
- Adviser or Faculty Sponsor (if applicable): Frank Scalzo
- If you are a graduate or undergraduate student, has your Adviser or Faculty Sponsor seen and approved your application?
  (x) Yes ( ) No
- Your Adviser's or Faculty Sponsor's email address (if applicable): scalzo@bard.edu
- Please list all individuals (full name and status, i.e. faculty, staff, student) involved in this project that will be working with human subjects. Note: Everyone listed must have completed Human Subject Research Training within the past three years. *
- Do you have external funding for this research? *
  (x) Yes ( ) No
- If so, state the name of the sponsor and the title of the project as it was submitted to that sponsor.

  Sponsors are yet to be found.

- **Section 2**

Please enter the following information about your project.

- What is the title of your project?

"Psilocybin and Music: A proposal to study the effects of music on efficacy of psilocybin-assisted therapy for treatment-resistant depression"

- When do you plan to begin this project? (Start date): 09/01/2024

- Describe your research question(s):

  Does listening to music during psilocybin-assisted therapy increase the therapy's effectiveness for treating treatment-resistant depression?

- Describe the population(s) you plan to recruit and how you plan to recruit participants. Please submit all recruitment material, emails and scripts to IRB@bard.edu

Participants will be recruited by sending the information about the study to general practitioners registered in New York State, who will then pass on the information, including contact information, to their patients. Willing candidates will then themselves initiate contact with the research team, will be sent additional information about the study, and a telephone screening will be arranged, in which the lead psychiatrist will obtain additional information about the patients, including demographics, medical conditions, and all the other excluding criteria

- Will your participants include individuals from vulnerable or protected populations (e.g., children, pregnant women, prisoners, or the cognitively impaired)? *

  ○ Yes ◉ no

- If your participants will include individuals from the above populations, please specify the population(s) and describe any special precautions you will use to recruit and consent.

- Approximately how many individuals do you expect to participate in your study? **

  30

- Describe the procedures you will be using to conduct your research. Include descriptions of what tasks your participants will be asked to do, and about how much time will be expected of each individual. NOTE: If you have supporting materials (printed surveys, questionnaires, interview questions, etc.), email these documents separately as attachments to IRB@bard.edu. Name your attachments with your last name and a brief description (e.g., "WatsonSurvey.doc).

The participants will take psilocybin, two times (10 and 25mgs respectively), with one group listening to music during the session, and the other not listening to music. Participants will be asked to complete Quick Inventory of Depressive Symptomatology, Beck Depression Inventory, and Snaith-Hamilton Pleasure Scale before the study and 6 times afterwards, for up to 3 months. Each participant will be expected to contribute 20 hours in total for the preparatory session and psilocybin-assisted therapy sessions, and about 10 more hours for taking measures, including baseline measures and the follow-ups. Though the commitment will last for months, including the follow-up measures.

- Describe any risks and/or benefits your research may have for your participants.

Risks: Given the type of experience that taking psilocybin usually is, there is a chance at experiencing major discomfort and distress. It is normal to feel distress during the experience, yet it might be very uncomfortable. It might involve feeling extremely anxious, fearful, and nervous. Additionally, there is a small chance of psychosis or having lasting changes in perception. If the experience gets so intense that the participant is no longer willing to go through it, they can ask the therapist to give them medication that will calm them down and reduce the intensity of the experience.

Benefits: Psilocybin has the potential to help those with treatment-resistant depression. Therefore, there is a chance that participants will directly benefit from participating in this study. In addition to direct benefits to them, they will help advance scientific research in the field, which will help in improving treatment options and helping more people.

- Describe how you plan to mitigate (if possible) any risks the participants may encounter.

Strict eligibility criteria: Exclusion criteria will include a history of being diagnosed with psychotic disorders, a history of immediate family members being diagnosed with psychotic disorders, any other medical condition which might render a candidate unsuitable for the study, history of suicide attempts, history of mania, blood or needle phobia, being pregnant at the time of screening or anytime afterwards, and current drug dependence.

Therapeutic assistance and tranquilizing drugs will be present during psilocybin sessions, and if necessary, will be administered to the participants. Psychiatrists will not only be always present during the sessions, but will also be available anytime afterwards, for 3 months, for consultations, discussions, and talks.
.

- Describe the consent process (i.e., how you will explain the consent form and the consent process to your participants):

I will explain to them that the consent form includes the information about the study: the purpose, procedures, risks, benefits, compensation, confidentiality. I will give them the document, ask them to read it in detail, underscore that they can take as much time as they need, and encourage them to ask me any questions that they might have. I will also make sure that they understand that signing the

consent form does not mean that they must complete the study – they can withdraw at any moment, for any reason, without owing an explanation.

- Have you prepared a consent form(s) and emailed it as an attachment to IRB@bard.edu?
  Note: You must submit all necessary consent forms before your proposal is considered complete. *
  (x) Yes ( ) No

- If you are collecting data via media capture (video, audio, photos), have you included a section requesting consent for this procedure(s) in your consent form(s)?
  ( ) Yes ( ) No (x) Not applicable

- If your project will require you to employ a verbal consent process (no written consent forms), please describe why this process is necessary and how verbal consent will be obtained and stored.

  My project employs written consent.

- What procedures will you use to ensure that the information your participants provide will remain confidential and safeguarded against improper access or dissemination?

  Information will be kept in an online vault.

- Will it be necessary to use deception with your participants at any time during this research?
  Withholding details about the specifics of one's hypothesis does not constitute deception, this is called incomplete disclosure. Deception involves purposefully misleading participants about the nature of the research question or about the nature of the task they will be completing. *
  ( ) Yes (x) No

- If your project study includes deception, please describe here the process you will use, why the deception is necessary, and a full description of your debriefing procedures.

- For all projects, please include your debriefing statement. (This is information you provide to the participant at the end of your study to explain your research question more fully than you may have been able to do at the beginning of the study.) All studies must include a debriefing statement. Be sure to give participants the opportunity to ask any additional questions they may have about the study

DEBRIEF

Study title:

Psilocybin and Music: A proposal to study the effects of music on efficacy of psilocybin-assisted therapy for treatment-resistant depression.

Principal Investigator:

Giorgi Gzirishvili

Purpose of the study:

The purpose of this study is to investigate the role of music in psilocybin-assisted therapy for treatment-resistant depression. This is done by comparing two groups of participants, those who listen to music during psilocybin-assisted therapy and those who do not.

Deception:

You were not informed about the fact that there are two groups, one that listens to music and one that does not. This was done to make sure that the results of the study are not affected by your expectations and thoughts about music's presence/absence.

Contact:

If you have any questions regarding this study, please do not hesitate to ask now or contact the principal investigator Giorgi Gzirishvili, email: gg9036@bard.edu. You can also contact the Institutional Review Board, email: irb@bard.edu.

- If you will be conducting interviews in a language other than English, will you conduct all of the interviews yourself, or will you have the assistance of a translator? If you will be using the assistance of a translator, that individual must also certify that he or she is familiar with the human subject protocol and has completed the online training course.

  ○ Myself ○ Translator ☒ Not applicable

- If your recruitment materials or consent forms will be presented in languages other than English, please translate these documents and email copies to IRB@bard.edu. I have submitted all of my translated materials.

  ○ Yes ○ No ☒ Not applicable

Appendix E:

Materials

Quick Inventory of Depressive Symptomatology (QIDS SR-16)

About: This scale is a self-report measure of depression.

Items: 16

Reliability: Internal consistency for the QIDS-SR_{16} = (Cronbach's α=0.86) QIDS-SR_{16} scores correlated highly with IDS-SR_{30} (.96) and HAM-D_{24} (.86) scores.

Validity: The QIDS-$SR_{16,}$ IDS-$SR_{30,}$ and HAM-D_{24}, had very similar sensitivity in detecting change in symptoms. This suggests these three scales have high concurrent validity.

Scoring:
Questions in the QIDS – SR-116 correlate with the nine DSM-IV symptom criterion domains, Including: Sleep disturbance (initial, middle, and late insomnia or hypersomnia) **(Q 1 - 4),** Sad mood **(Q 5),** Decrease/increase in appetite/weight **(Q 6 - 9),** Concentration **(Q 10)**, Self-criticism **(Q 11),** Suicidal ideation **(Q 12),** Interest **(Q 13),** Energy/fatigue **(Q 14),** Psychomotor agitation/retardation **(Q 15 - 16).**

Scoring Instructions:

1. Enter the highest score on any 1 of the 4 sleep items (1-4) _____
2. Enter score on item 5 _____
3. Enter the highest score on any 1 of the appetite/weight items (6-9) _____
4. Enter score on item 10 _____
5. Enter score on item 11 _____
6. Enter score on item 12 _____
7. Enter score on item 13 _____
8. Enter score on item 14 _____
9. Enter the highest score on either of the 2 psychomotor items (15 and 16) _____
10. Sum the item scores for a total score. Total score range 0-27. _____

Severity of depression can be judged based on the total score.

1-5 = No depression
6-10 = Mild depression
11-15 = Moderate depression
16-20 = Severe depression
21-27 = Very severe depression

References:

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. K., … Keller, M. B. (2003). The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biological Psychiatry, 54,* 573-583.

http://www.ids-qids.org/Scoring_Instructions.pdf

http://www.ids-qids.org/index2.html#table2

Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR16)

NAME: TODAY'S DATE:

Please circle the one response to each item that best describes you for the past seven days.

1. Falling Asleep:
   - 0 I never take longer than 30 minutes to fall asleep.
   - 1 I take at least 30 minutes to fall asleep, less than half the time.
   - 2 I take at least 30 minutes to fall asleep, more than half the time.
   - 3 I take more than 60 minutes to fall asleep, more than half the time.
2. Sleep During the Night:
   - 0 I do not wake up at night.
   - 1 I have a restless, light sleep with a few brief awakenings each night.
   - 2 I wake up at least once a night, but I go back to sleep easily.
   - 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.
3. Waking Up Too Early:
   - 0 Most of the time, I awaken no more than 30 minutes before I need to get up.
   - 1 More than half the time, I awaken more than 30 minutes before I need to get up.
   - 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
   - 3 I awaken at least one hour before I need to, and can't go back to sleep.
4. Sleeping Too Much:
   - 0 I sleep no longer than 7–8 hours/night, without napping during the day.
   - 1 I sleep no longer than 10 hours in a 24-hour period including naps.
   - 2 I sleep no longer than 12 hours in a 24-hour period including naps.
   - 3 I sleep longer than 12 hours in a 24-hour period including naps.

Enter the highest score on any 1 of the 4 sleep items (1–4 above) ____

5. Feeling Sad:
   - 0 I do not feel sad
   - 1 I feel sad less than half the time.
   - 2 I feel sad more than half the time.
   - 3 I feel sad nearly all of the time.
6. Decreased Appetite:
   - 0 There is no change in my usual appetite.
   - 1 I eat somewhat less often or lesser amounts of food than usual.
   - 2 I eat much less than usual and only with personal effort.
   - 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.
7. Increased Appetite:
   - 0 There is no change from my usual appetite.

1 I feel a need to eat more frequently than usual.
2 I regularly eat more often and/or greater amounts of food than usual.
3 I feel driven to overeat both at mealtime and between meals.

8. Decreased Weight (Within the Last Two Weeks):
0 I have not had a change in my weight.
1 I feel as if I've had a slight weight loss.
2 I have lost 2 pounds or more.
3 I have lost 5 pounds or more.

9. Increased Weight (Within the Last Two Weeks):
0 I have not had a change in my weight.
1 I feel as if I've had a slight weight gain.
2 I have gained 2 pounds or more.
3 I have gained 5 pounds or more.

Enter the highest score on any 1 of the 4 appetite/weight change items (6–9 above) ____

10. Concentration/Decision Making:
0 There is no change in my usual capacity to concentrate or make decisions.
1 I occasionally feel indecisive or find that my attention wanders.
2 Most of the time, I struggle to focus my attention or to make decisions.
3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:
0 I see myself as equally worthwhile and deserving as other people.
1 I am more self-blaming than usual.
2 I largely believe that I cause problems for others.
3 I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:
0 I do not think of suicide or death.
1 I feel that life is empty or wonder if it's worth living.
2 I think of suicide or death several times a week for several minutes.
3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest:
0 There is no change from usual in how interested I am in other people or activities.
1 I notice that I am less interested in people or activities.
2 I find I have interest in only one or two of my formerly pursued activities.
3 I have virtually no interest in formerly pursued activities.

14. Energy Level:
0 There is no change in my usual level of energy.
1 I get tired more easily than usual.
2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).

3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:
    0 I think, speak, and move at my usual rate of speed.
    1 I find that my thinking is slowed down or my voice sounds dull or flat
    2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
    3 I am often unable to respond to questions without extreme effort.
16. Feeling Restless:
    0 I do not feel restless.
    1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.
    2 I have impulses to move about and am quite restless.
    3 At times, I am unable to stay seated and need to pace around.

Enter the highest score on either of the 2 psychomotor items (15 or 16 above) ____

Total Score:____ (Range 0–27)

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.
- 0 I do not feel sad.
- 1 I feel sad
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.
- 0 I don't cry any more than usual.
- 1 I cry more now than I used to.
- 2 I cry all the time now.
- 3 I used to be able to cry, but now I can't cry even though I want to.

11.
0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.
0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.
0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.
0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.
0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score_____Levels of Depression

1-10_____These ups and downs are considered normal
11-16_____ Mild mood disturbance
17-20_____Borderline clinical depression
21-30_____Moderate depression
31-40_____Severe depression
over 40_____Extreme depression

http://www.med.navy.mil/sites/NMCP2/PatientServices/SleepClinicLab/Documents/Beck_Depression_Inventory.pdf

Snaith-Hamilton Pleasure Scale (SHAPS)

(Snaith et al., 1995)

Rated on a 4-point Likert scale: 0 = strongly disagree, 1 = disagree, 2 = agree, 3 = strongly agree, except for items marked with *, which are reverse coded with answer choices as follows: definitely agree, agree, disagree, and strongly disagree

1. I would enjoy my favourite television or radio programme.
* 2. I would enjoy being with my family or close friends.
3. I would find pleasure in my hobbies and pastimes.
* 4. I would be able to enjoy my favourite meal.
* 5. I would enjoy a warm bath or refreshing shower.
6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread.
* 7. I would enjoy seeing other people's smiling faces.
8. I would enjoy looking smart when I have made an effort with my appearance.
* 9. I would enjoy reading a book, magazine or newspaper.
10. I would enjoy a cup of tea or coffee or my favorite drink.
11. I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend.
12. I would be able to enjoy a beautiful landscape or view.
13. I would get pleasure from helping others.
14. I would feel pleasure when I receive praise from other people.

Scoring: Items marked with * are reverse coded with answer choices as follows: definitely agree, agree, disagree, and strongly disagree. All other items are simply sum-scored.

https://datashare.nida.nih.gov/instrument/snaith-hamilton-pleasure-scale

Snaith, R.P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry, 167*(1), 99-103.

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel. It is not a diagnostic test.

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major psychiatric disorders in DSM-5 and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. Clinicians can use it, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis or diagnoses is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, questions J2b or K6b).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either YES or NO. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. has questions that investigate these issues.

For any questions, suggestions, need for a training session or information about updates of the M.I.N.I., please contact:
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A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO IN THE DIAGNOSTIC BOX, AND MOVE TO THE NEXT MODULE)

A1	a	Were you ever depressed or down, or felt sad, empty or hopeless most of the day, nearly every day, for two weeks?	NO	YES
		IF NO, CODE NO TO **A1b**: IF **YES** ASK:		
	b	For the past two weeks, were you depressed or down, or felt sad, empty or hopeless most of the day, nearly every day?	NO	YES
A2	a	Were you ever much less interested in most things or much less able to enjoy the things you used to enjoy most of the time, for two weeks?	NO	YES
		IF NO, CODE NO TO **A2b**: IF **YES** ASK:		
	b	In the past two weeks, were you much less interested in most things or much less able to enjoy the things you used to enjoy, most of the time?	NO	YES
			➡	
		IS **A1a** OR **A2a** CODED **YES**?	NO	YES

			Past 2 Weeks		Past Episode	
A3		IF **A1b** OR **A2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE IF **A1b** AND **A2b** = **NO**: EXPLORE **ONLY** THE MOST SYMPTOMATIC **PAST** EPISODE.				
		Over that two week period, when you felt depressed or uninterested:				
	a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lb or ± 3.5 kg, for a 160 lb/70 kg person in a month)? IF **YES** TO EITHER, CODE **YES**.	NO	YES	NO	YES
	b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
	c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day? Did anyone notice this?	NO	YES	NO	YES
	d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
	e	Did you feel worthless or guilty almost every day?	NO	YES	NO	YES
		IF **YES**, ASK FOR EXAMPLES. LOOK FOR DELUSIONS OF FAILURE, OF INADEQUACY, OF RUIN OR OF GUILT, OR OF NEEDING PUNISHMENT OR DELUSIONS OF DISEASE OR DEATH OR NIHILISTIC OR SOMATIC DELUSIONS. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. Current Episode ☐ No ☐ Yes Past Episode ☐ No ☐ Yes				
	f	Did you have difficulty concentrating, thinking or making decisions almost every day?	NO	YES	NO	YES
	g	Did you repeatedly think about death **(FEAR OF DYING DOES NOT COUNT HERE)**, or have any thoughts of killing yourself, or have any intent or plan to kill yourself? Did you attempt suicide? **IF YES TO EITHER, CODE YES.**	NO	YES	NO	YES
A4		Did these symptoms cause significant distress or problems at home, at work, at school, socially, in your relationships, or in some other important way, and are they a change from your previous functioning?	NO	YES	NO	YES

A5 In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any significant depression or any significant loss of interest? N/A NO YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES** AND IS **A4** CODED **YES** FOR THAT TIME FRAME?

AND

IS "RULE OUT ORGANIC CAUSE (**O2** SUMMARY)" CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT AND / OR PAST.

IF **A5** IS CODED **YES,** CODE **YES** FOR RECURRENT.

NO **YES**

MAJOR DEPRESSIVE EPISODE

CURRENT ☐
PAST ☐
RECURRENT ☐

A6 a How many episodes of depression did you have in your lifetime? _____

Between each episode there must be at least 2 months without any significant depression.

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