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Influence of openness on the hedonic experience after ketamine administration

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Christina Bieglmayer BSc

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Betreut von | Supervisor:	Univ.-Prof. Dipl.-Psych. Dr. Helmut Leder
Mitbetreut von | Co-Supervisor:	Mag. Dr. Julia Sophia Crone

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Introduction

Imagine the following situation: You are listening to one of your favourite songs, immersing yourself in the melody, experiencing the rhythm, and feeling the emotion it evokes. Listening to music can induce pleasurable or hedonic experiences (Reybrouck & Eerola, 2022). However, not everyone is able to experience pleasure when listening to music (Zatorre, 2015).

This diminished capacity to experience pleasure from previously rewarding activities is called anhedonia, a symptom prevalent in various neuropsychiatric disorders, including posttraumatic stress disorder (Armour et al., 2015), major depressive disorder (MDD; Loas, 1996), schizophrenia (Horan et al., 2006), bipolar disorder (Mazza et al., 2009; Sanacora et al., 2017), and substance use disorder (Hatzigiakoumis et al., 2011). Notably, the level of anhedonia symptom burden differs according to the specific diagnosis, with evidence suggesting that it is more pronounced in ongoing MDD than in other types of disorders (Trøstheim et al., 2020).

Depressive disorders are one of the leading causes of disability around the world (World Health Organization [WHO], 2022). According to the WHO, approximately 280 million individuals around the world are living with depressive disorders, representing about 3.8% of the population (WHO, 2021). In many cases, depression presents as a chronic and recurrent condition that significantly impairs the well-being of those affected and their families (Alonso et al., 2004; ten Have et al., 2018). Furthermore, individuals who experience depression require a considerable amount of healthcare resources compared to those who do not, resulting in a significant medical and economic burden to society (Jain et al., 2022; Lépine & Briley, 2011).

In order to be diagnosed with depression, at least five symptoms must be present and persist for a minimum of two weeks. These symptoms must include either anhedonia or a depressed mood (American Psychiatric Association [APA], 2015). Consequently, anhedonia represents a main symptom of depression, with approximately 70% of individuals diagnosed with depression showing symptoms of anhedonia (Cao et al., 2019b). Psychological and pharmacological treatments, including standard pharmacological treatments such as selective serotonin reuptake inhibitors, have been demonstrated to reduce negative affect (e.g., depressed mood) and associated functional impairments, but do not appear to address deficits in positive affect, such as the reduced ability to feel pleasure (Dunn et al., 2020; Watanabe et al., 2022). Anhedonia can therefore persist in individuals with a depressive disorder despite improvements in other symptoms, affecting their overall quality of life (Cao et al., 2019b;

Vinckier et al., 2017). Due to the dangers of anhedonia and the suboptimal anti-anhedonic effects of many available antidepressants, there is an urgent need to investigate the efficacy of newer treatments specifically targeting this condition (Cao et al., 2019a).

A promising compound has emerged from research into psychoactive substances: Ketamine, a glutamate antagonist, has been associated with a fast-acting anti-anhedonic effect and a restorative hedonic effect in patients with depression (Lally et al., 2015, Saland et al., 2016). However, the use of ketamine may be associated with potentially negative side effects, which include transient dissociative and psychotomimetic effects as well as cardiovascular symptoms, especially increased blood pressure (Ceban et al., 2021). Another important risk of using ketamine is the potential for abuse and dependence (Sassano-Higgins et al., 2016). Although ketamine is less addictive than some other drugs, the potential for abuse and dependence remains (Widnyana et al., 2023). The incidence of serious adverse events and/or permanent medical consequences reported in clinical trials is low; however, the available data on long-term safety remains limited (McIntyre et al., 2021; Singh et al., 2016).

Given the risk-benefit ratio of ketamine, careful consideration should be given to which individuals are most likely to benefit from its use (Dale et al., 2020; Sanacora et al., 2017). Consequently, the identification of pretreatment predictors that influence the antidepressant and, specifically, the anti-anhedonic effects of ketamine is essential (Meshkat et al., 2023). Research into the predictive factors for the safety, tolerability, and efficacy of ketamine treatment highlights the importance of identifying clinical, biochemical, and psychosocial predictors prior treatment (Iadarola et al., 2015). Studies have demonstrated that variables such as genetic markers and clinical markers, including a history of suicide, are significant (Rong et al., 2018). However, there is also growing evidence that psychosocial factors, including personality differences, may influence treatment outcomes (Kudo et al., 2017; Shao & Zhu, 2020).

Research repeatedly shows a relationship between personality traits and depression, with depressed patients typically exhibiting high levels of neuroticism and low levels of extraversion and conscientiousness (Kotov et al., 2010). However, the relationship between openness and depression remains ambiguous, with studies reporting conflicting results (Takahashi et al., 2013). While initial findings suggested an association between openness and depression, further analysis showed that openness was no longer a significant predictor of depression when other personality factors such as neuroticism and extraversion were taken into account. However, research has shown that openness is associated with anhedonia, with openness remaining a significant predictor of anhedonia even after controlling for other

personality traits, suggesting a stronger association with this specific symptom of depression than with depression in general (Khoo & Simms, 2018). In particular, a negative correlation has been found between openness and anhedonia, meaning that higher levels of openness are associated with lower levels anhedonia (Ross et al., 2002). Furthermore, research has demonstrated that openness is a notable predictor of a positive response to ketamine treatment (Dale et al., 2020). Higher levels of openness are associated with reduced anxiety-related symptoms during ketamine treatment and a more favorable subjective experience of ketamine, which contributes to its therapeutic efficacy (Aust et al., 2019). These findings align with research suggesting that a positive subjective ketamine experience, characterized by reduced anxiety and a pleasant altered state of consciousness, can enhance therapeutic outcomes (Aday et al., 2021; Passie et al., 2021).

Considering the goal of personalized medicine and treatment, it is important to identify predictors that contribute to the restoration of regular hedonic function. To this end, studies with healthy subjects are needed to gain a basic understanding of the potential predictors of the pro-hedonic effects of ketamine and to provide a basis for future research into the treatment of anhedonia. Investigating whether personality traits, particularly openness, influence hedonic experience and interact with ketamine treatment is a crucial first step in understanding the potential impact of personality on ketamine's efficacy.

Pleasure

A crucial aspect of human life is the pursuit of personal well-being (Huta & Ryan, 2010). Well-being is commonly understood to comprise two components: hedonia (focusing on pleasure and enjoyment) and eudaimonia (focusing on growth and meaning; Huta & Waterman, 2014; Kashdan et al., 2008). Although philosophers and psychologists have differed in their definitions, most agree that hedonia refers to a state of pleasure (Berridge & Kringelbach, 2011). Consequently, hedonic experiences that provide pleasure are evidently an important, salient, and frequent aspect of daily life, essential for healthy psychological functioning and overall well-being (Berridge & Kringelbach, 2008; Snaith et al., 1995). However, in affective disorders there may be a pathological absence of hedonic experiences, known as anhedonia (Berridge & Kringelbach, 2015).

Anhedonia as one Symptom of Depression

According to the APA (2015), anhedonia is a cardinal symptom of depression and is defined as “markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day” (p.160). While other symptoms including changes in appetite or weight, difficulty concentrating, and sleep disturbances are also significant (APA, 2015), anhedonia has received increased empirical and theoretical investigation due to its profound impact on patients' quality of life and functional outcomes in depression (Serretti, 2023).

Anhedonia has been shown to be a predictor of poorer prognosis in patients with depressive disorders, including higher overall disease severity, longer duration of depressive episodes, and a greater number of depressive episodes (Ely et al., 2021; Gabbay et al., 2015; Vrieze et al., 2013). Anhedonia is also associated with a poorer response to treatment (Vrieze et al., 2014) and a longer time to remission (McMakin et al., 2012). Importantly, studies have found significant correlations between anhedonia severity and suicidal ideation and behavior (Ducasse et al., 2018; Winer et al., 2014). Furthermore, it has been shown that anhedonia can persist after conventional psychopharmacological and psychotherapeutic treatments, even if other symptoms have disappeared (Boyer et al., 2000; Nutt et al., 2007). In accordance with this, research has demonstrated that traditional medical treatments for depression including selective serotonin reuptake inhibitors, have limited effectiveness in alleviating symptoms of anhedonia and may also result in adverse effects such as emotional blunting and sexual dysfunction (Fagiolini et al., 2021; Montejo et al., 2019).

Despite the growing recognition of anhedonia and its influence on depression, there is no consensus on a universally accepted definition or a comprehensive understanding of its neurobiological underpinnings and contributing factors (Llorca & Gourion, 2015; Treadway & Zald, 2011). In particular, Ribot's (1896) initial conceptualization of anhedonia, which was primarily concerned with the absence of pleasure, has been criticised for its narrow focus on subjective experience and its inability to differentiate between the different dimensions of the condition (Berridge & Kringelbach, 2008). Indeed, recent literature on pleasure demonstrates that the lack of experiencing pleasure is only one aspect of anhedonia (Rømer Thomsen et al., 2015; Treadway & Zald, 2011). Consequently, anhedonia represents a much more complex phenomenon than the hedonic experience alone, resulting in a shift in focus to the multifaceted nature of anhedonia (Ho & Sommers, 2013).

Conceptualization of Anhedonia

The investigation of human behavior frequently considers actions aimed at achieving rewards or pleasurable outcomes—a perspective that is particularly relevant in understanding symptoms observed in depression (Halahakoon et al., 2020). Anhedonia is typically characterized as a deficit in the reward pathways of the brain and is closely related to aspects such as reward evaluation, decision-making, anticipation, and motivational states (Der-Avakian & Markou, 2012; Liang et al., 2022).

The term "reward*"* is often used as an umbrella term encompassing a wide variety of stimuli that evoke a positive emotional state, and a unitary process whereby reward-related stimuli are transformed into a state of pleasure (Berridge & Kringelbach, 2008). Nevertheless, the process of reward is a complex phenomenon, involving a number of psychological components and neurobiological mechanisms (Berridge et al., 2009). A common distinction of the reward system consists of the following subtypes: reward wanting, reward liking, and reward learning (Berridge & Kringelbach, 2015; Borsini et al., 2020). Reward wanting is related to the motivation for a reward or the stimulating effect of a reward. Reward liking refers to the actual hedonic experience and pleasure of the reward itself. Reward learning involves "associations, representations, and predictions about future rewards based on past experiences" (Berridge & Kringelbach, 2008, p.458). Anhedonia can therefore be understood as a disorder within each of these components reflecting "impairments in the ability to experience, pursue and/or learn about pleasure" (Rømer Thomsen et al., 2015, p.2). Consistent with this reasoning, Treadway and Zald (2011) suggested to distinguish between motivational, consummatory, and decisional aspects in the definition of anhedonia.

Furthermore, there is compelling evidence that different neuroanatomical and neurochemical processes are involved in the reward system (Rømer Thomsen et al., 2015). Focusing on the two domains of reward wanting and reward liking, it can be observed that the regulation of wanting is primarily controlled by the mesocorticolimbic system of the brain (Berridge & Kringelbach, 2015). This system includes dopamine projections from the midbrain to target structures in the forebrain, such as the nucleus accumbens and other parts of the striatum (Berridge & Robinson, 2016). Whereas, the generation of pleasurable responses, or liking, is mainly attributed to the opioid and endocannabinoid systems, particularly at specific areas known as "hedonic hotspots" (Berridge et al., 2009; Mahler et al., 2007; Peciña et al., 2006). These hotspots are found in the limbic prefrontal cortex, orbitofrontal, and insular regions, as well as in deeper subcortical regions such as in specific

parts of the nucleus accumbens and the ventral pallidum (Kringelbach et al., 2003; Small et al., 2001).

However, it is important to note that this conceptualization of the reward system may not always be applicable to behavior, as the various aspects of reward processes can influence each other and occur simultaneously (Rizvi et al., 2016). Furthermore, their networks show some degree of overlap, each involving a complex network of brain regions that is not yet fully understood (Borsini et al., 2020; Ding et al., 2023). Nonetheless, a better understanding of the reward components is crucial, as deficiencies in each component can result in distinct expressions or subtypes of anhedonia and may vary depending on the psychiatric disorder (Liu et al., 2021; Rømer Thomsen, 2015).

Importance of Hedonic Experiences

Research indicates that the wanting and learning components are more easily impaired in patients with depression, while the capacity for liking responses in the brain is relatively robust (Rømer Thomsen et al., 2015). In line with this, studies have shown that the wanting aspect of anhedonia is most clearly related to depression (Franzen & Brinkmann, 2016; Sherdell et al., 2012). Furthermore, existing literature on anhedonia has demonstrated that individuals with depression can exhibit hedonic reactions to sensory stimuli that are similar to those observed in healthy controls (Clepce et al., 2010; Germans & Kring, 2000; Swiecicki et al., 2009). Supporting this observation, Dichter et al. (2010) reported that hedonic responses to sweet flavors were comparable between individuals with depression and those in the control group. It is important to note that most studies only used unimodal stimuli and primary rewards, mainly in the form of taste stimuli. However, the ability to feel pleasure encompasses a wide range of emotional, social, and physical experiences (Kringelbach, 2005; Kringelbach & Berridge, 2009). Furthermore, hedonic responses can be induced by a range of sensory stimuli that have no direct link to survival (Zeki, 2013).

Thus, the traditional use of primary rewards, mostly in the form of taste stimuli, to assess an individual's ability to experience pleasure may represent an overly simplistic and under-representative approach that does not fully capture the range of human ability to experience pleasure (Rizvi et al., 2016). Illustrating the limitations of this approach, McFarland et al. (2009) conducted a study in a more complex setting using different stimuli such as puzzles and found that individuals with depression reported reduced emotional responsiveness to pleasant stimuli. Nevertheless, the paucity of literature exploring complex

hedonic experiences highlights the need to use more complex stimuli to investigate their effects on the dimensions of anhedonia, particularly in relation to hedonic experiences. Such investigations are crucial for enhancing our understanding of hedonic processing, its driving forces, and its implications for human behavior, which could further inform the development of treatment strategies for depression and anhedonia (Berridge, 2003).

Aesthetic stimuli such as music and visual art are examples of stimuli that can create a more realistic and complex hedonic experience (Clemente et al., 2023). Psychological perspectives consider aesthetic experiences as a rewarding process, proposing a connection between aesthetic experience and pleasure (Leder et al., 2004; Silvia, 2005). Given the pervasive influence of audiovisual culture on our lives, it seems probable that aesthetic stimuli such as music or visual art are integrated into our environment, our daily experiences, and the pleasures we derive from them (Tiihonen et al., 2017). According to Salimpoor et al. (2009), music differs from other reward stimuli in that "it has no clearly established biological value (c.f., food, love and sex), no tangible basis (c.f., pharmacological drugs and monetary rewards) and no known addictive properties (c.f., gambling and nicotine)" (p.1). Nevertheless, music consistently ranks as one of the most pleasurable experiences for humans, making it an intriguing stimulus for hedonic research (Dubé & Le Bel, 2003).

The Use of Music to induce Hedonic Experiences

Music has played a significant role in human culture throughout history, serving as one of the few cultural universals that evokes a wide range of emotions (Chanda & Levitin, 2013; Grewe et al., 2007). Its ubiquitous presence in people's lives not only indicates the pleasure and sense of reward it brings, but also highlights its importance as one of the most universally pleasurable stimuli (Nemati et al., 2019; Salimpoor et al., 2009). Research supports this, showing that listening to music is one of the most pleasurable and rewarding experiences (Blood & Zatorre, 2001; Dubé & Le Bel, 2003). Although the perception of music is demanding, complex, and abstract, music-related pleasure has been linked to the reward system in a similar way to other pleasurable activities such as food and sex (Salimpoor et al., 2011). For instance, a meta-analysis comparing the neural correlates of pleasure induced by music and food found that both types of reward engage overlapping regions within the reward circuitry (Mas-Herrero et al., 2021). Similarly, a study involving preadolescents showed that music consistently activates reward-related brain regions, particularly the medial orbitofrontal

and ventromedial prefrontal cortices, which are integral to both musical pleasure and general reward experiences (Fasano et al., 2023).

Furthermore, music-induced reward can be categorized into the subtypes mentioned previously, including an anticipation or wanting phase for a particular rewarding musical structure, a consummatory or liking phase for the musical reward, which may lead to a peak of pleasure, and a satiation or learning phase in which one learns and actualizes musical predictions (Brattico et al., 2013; Gebauer et al., 2012). In line with this, Salimpoor (2011) demonstrated that anticipating an abstract reward, such as music, can lead to dopamine release in an anatomical pathway that is distinct from that associated with the actual peak of pleasure. Specifically, the caudate nucleus was activated during anticipation, while the nucleus accumbens was more active during the peak of emotional responses to music. In addition, it has been shown that individuals with MDD have lower activity in the left nucleus accumbens when listening to music compared to healthy controls, suggesting that the depressive state leads to altered processing of music-induced reward in critical neural reward circuits (Jenkins et al., 2018).

It should be emphasized that the emotional and pleasurable effects of music are partially dependent on cultural and personal preferences, which can result in different experiences of music from one individual to another (Mas-Herrero et al., 2021). Therefore, measuring the effect of music can be challenging due to the lack of objective experimental variables capable of capturing subjective experiences of pleasure and emotion (de Fleurian & Pearce, 2021). However, physiological changes known as chills often occur during moments of intense pleasure and can be used to capture the state of pleasure and hedonic experiences (Salimpoor et al., 2011). This phenomenon is particularly relevant to music, which is one of the most commonly reported chill-inducing stimulus (Goldberg, 1990). Chills represent an intense psychophysical reaction characterized by a strong arousal of the autonomic nervous system, which is often accompanied by measurable physical changes, such as an increase in skin conductance or heart rate, and sensations such as trembling or tingling along the spine (Bignardi et al., 2022; Grewe et al., 2009). For example, Sumpf et al. (2015) demonstrated that the chills evoked by music and film stimuli are associated with intense pleasurable emotional responses and increased physiological arousal, including a rise in heart rate. Similarly, it was found that music-induced chills led to increased autonomic arousal, as measured by skin conductance (Klepzig et al., 2020). Thus, chills provide an objective means of assessing a subjective experience such as pleasure, which are otherwise challenging to operationalize (de Fleurian & Pearce, 2021; Salimpoor et al., 2011).

Ketamine

In recent years, the therapeutic benefits of psychedelic drugs have garnered increasing interest in both the scientific community and clinical practice (Sial et al., 2020). Notably, ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a promising new treatment option for treatment-resistant depression (TRD; Muscat et al., 2021). Although not classified as a traditional psychedelic but rather as a dissociative anesthetic, ketamine possesses psychoactive properties that can induce an altered state of consciousness (Johnston et al., 2023; Vollenweider & Kometer, 2010).

Ketamine is a racemic mixture comprising of two optical enantiomers: R-ketamine and S-ketamine (Paul et al., 2009). Initially discovered in the 1960s as an anaesthetic, it has recently garnered attention as a promising treatment for MDD due to its fast-acting antidepressant and anti-anhedonic effects (Nogo et al., 2022; Yavi et al., 2022). However, the clinical use of ketamine in treating depression is constrained by its requirement for intravenous administration, which limits its applicability in outpatient settings (Daly et al., 2018). In 2019 and 2020, esketamine, the S-enantiomer of ketamine, was approved by the U.S. Food and Drug Administration as an intranasal formulation for the treatment of TRD and MDD with suicidal ideation (Gastaldon et al., 2019; Yavi et al., 2022). However, a recent meta-analysis comparing the antidepressant effects of ketamine and esketamine demonstrated that ketamine offers superior benefits in terms of rapid onset and sustained treatment effects, emphasizing its potential therapeutic advantages (Nikolin et al., 2023).

Therapeutic Effects

The potential antidepressant properties of ketamine were first discovered in an animal study by Sofia and Harakal (1975), who observed that oral administration of the drug mitigated symptoms similar to those alleviated by traditional antidepressants. Against a background of limited studies in rodents suggesting that NMDA receptor antagonists influence MDD (Layer et al., 1995; Nowak et al., 1996), Berman and colleagues (2000) investigated the antidepressant properties of ketamine in a double-blind, placebo-controlled human trial, reporting that a single subanaesthetic dose of ketamine produced rapid and robust antidepressant effects. Subsequent randomized, placebo-controlled trials have consistently demonstrated the efficacy of subanaesthetic doses of ketamine in rapidly and significantly alleviating depressive symptoms in MDD (Kadriu et al., 2021). In addition, ketamine has shown effectiveness in individuals with TRD, who do not typically respond to

conventional antidepressants (Maurizio et al., 2020). Several randomized controlled trials have confirmed these findings, demonstrating that 60–70% of patients with TRD respond to ketamine treatment (Murrough et al., 2013; Zarate et al., 2006). Compared to conventional antidepressant drugs, ketamine exhibits a rapid onset of action, typically within 2 to 4 hours of administration (Hasselmann, 2014). Later studies have confirmed the rapid onset following a single injection, with antidepressant effects lasting from several days to over a week in some patients (Kim et al., 2023). Furthermore, repeated infusions of ketamine have been shown to produce a cumulative and more prolonged antidepressant effect compared to a single administration (Phillips et al., 2019). However, it is important to note that the psychoactive effect of ketamine often allows participants to discern whether they are receiving ketamine or a placebo, which could potentially influence the results (Wilkinson et al., 2019). To maintain blinding and mask the psychoactive effects, Lii et al. (2023) randomly assigned participants diagnosed with moderate to severe depression and scheduled for routine surgery to receive either a dose of ketamine or a placebo administered during the surgical procedure. The results showed that both groups had a comparable improvement in depression symptoms, raising the question of whether it was the pharmacological effects or the psychological effects (e.g., positive expectations and hope) that led to the improvement in symptoms.

Recent research has highlighted not only the efficacy of ketamine in alleviating general depressive symptoms but also its potential to reduce anhedonic symptoms (Rodrigues et al., 2020; Słupski et al., 2020). In line with this, a comprehensive meta-analysis, incorporating both human and preclinical studies, has demonstrated ketamine's potential to reverse consummatory and anticipatory reward deficits, highlighting its effectiveness and versatility as a treatment for the different subtypes of anhedonia (Nogo et al., 2022). Furthermore, a study investigating the hedonic sensitivity to low-dose ketamine demonstrated that ketamine can enhance the hedonic experience (Saland et al., 2016). Similar to its rapid antidepressant effect, ketamine also exhibited a rapid and significant reduction in anhedonia, with the effect being significant within 40 minutes and lasting for several days after the infusion (Lally et al., 2015). Beyond its rapid antidepressant and pro-hedonic effects, ketamine distinguishes itself from conventional antidepressants in its mechanism of action, showing efficacy even in patients unresponsive to other treatments (Matveychuk et al., 2020).

Underlying Mechanisms of Action

In contrast to conventional antidepressants, which primarily influence monoamine signaling, ketamine functions as a non-competitive antagonist of NMDA receptors within the glutamatergic system (Hillhouse & Porter, 2015). Beyond its action on the NMDA receptors, ketamine also interacts with various other receptor types including opioidergic, monoaminergic, cholinergic, and muscarinic receptors (Mion & Villevieille, 2013). Therefore, the multifaceted pharmacological actions of ketamine may explain its efficacy in alleviating anhedonia and its different subtypes, particularly in cases where conventional treatments are either ineffective or exacerbate anhedonic symptoms (Nogo et al., 2022).

The pharmacology of ketamine is complex, and its precise mechanisms of action are not yet fully understood, as it involves multiple actions contributing to its rapid antidepressant and pro-hedonic effects (Li et al., 2010). Ketamine interacts with multiple receptor types and notably inhibits NMDA receptors on GABAergic interneurons, resulting in elevated glutamate levels (Vesna et al., 2021). This surge in glutamate activates a cascade of mechanisms, including the stimulation of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and brain-derived neurotrophic factor (BDNF) release, which in turn activate subsequent intracellular signaling pathways, such as the mTORC1 pathway (Deyama & Duman, 2020). These effects of ketamine via direct inhibition of NMDA receptors, which indirectly enhances AMPA receptor function and affects neurotrophic signaling pathways, appear to serve as important triggers of adaptive neuronal plasticity at multiple levels, including synaptic, structural, and functional plasticity (Aleksandrova & Phillips, 2021). For example, Li et al. (2010) demonstrated that a single dose of ketamine can rapidly activate the mTOR signaling cascade, resulting in an increase in both the number and functionality of synapses in the prefrontal cortex of rodents.

Chronic stress or pathophysiological mechanisms including inflammation can induce impaired synaptic connections (Yates et al., 2021). This impairment is critical because neuroplasticity, which involves the reorganization of synapses in response to environmental stressors or rewards, is essential for adaptation, learning, and memory processes (Warraich & Kleim, 2010). Consequently, deficits in neuroplasticity may be linked to depression-like behaviors, potentially underpinning the persistence of depressive symptoms such as anhedonia (Price & Duman, 2020). According to a review by Niciu et al. (2014), ketamine is believed to increase synaptic plasticity in various brain regions related to depression, such as the prefrontal cortex, anterior cingulate cortex, amygdala, and hippocampus, thereby improving neural connectivity and brain complexity. In line with this, Kopelman et al. (2023)

observed that changes in neuroplasticity were associated with the treatment response to a single dose of ketamine in a sample of randomized patients with depression. Furthermore, ketamine has demonstrated an anti-anhedonic effect that occurs independently of general antidepressant symptoms and is associated with increased BDNF and mTOR protein expression, a critical factor in neuronal plasticity (Singh et al., 2023).

Thus, fast-acting, pro-hedonic properties of ketamine might be attributed to its modulation of brain complexity, specifically through enhanced neuroplasticity, resulting in improved information integration (Wang et al., 2023; Yates et al., 2021). This is particularly relevant for hedonic experiences elicited by music, which encompass a broad range of associative contexts, cognitive processes, and emotional cascades, all underpinned by intricate information integration (Brattico et al., 2013). Consequently, the evaluation of musical rewards involves the activation of diverse intrinsic processes characterized by substantial information integration (Carpentier et al., 2020).

Side Effects and Risks

Ketamine has shown promising effects in alleviating depressive symptoms, including the restoration of normal hedonic experiences (Saland et al., 2016; Widnyana et al., 2023). However, a systematic review by Short et al. (2018) highlights that the use of ketamine as an antidepressant is not without risk, identifying multiple side effects such as psychotomimetic reactions (e.g., dissociation and hallucinations), psychiatric disturbances (e.g., anxiety and euphoria), and neurological or cognitive impairments (e.g., poor memory and confusion). Cardiovascular risks such as increased blood pressure and heart rate have also been reported, as well as other symptoms such as nausea. Although these side effects are generally mild, dose-dependent, and transient, emerging shortly after administration and diminishing soon after, the potential for misuse and dependence cannot be overlooked (Acevedo-Diaz et al., 2020; Ceban et al., 2021; Sassano-Higgins et al., 2016). Notably, since the 1980s and 1990s, ketamine has become widely recognized globally as a club drug, commonly used in dance scenes (Kalsi et al., 2011). The misuse of ketamine as a recreational drug raises significant concerns regarding its risk of abuse when prescribed for the treatment of depression (Le et al., 2022).

Ketamine is known for its rapid antidepressant effects, which can be observed within hours or days of administration (Krystal et al., 2013). However, these effects tend to be transient, and the improvements usually disappear within a week, requiring frequent

treatments to maintain the observed benefits (Phillips et al., 2019). Nevertheless, there is a notable lack of long-term safety data concerning its use in the treatment of affective disorders (McIntyre et al., 2021; Short et al., 2018). In other adult populations, including patients with chronic pain, repeated use of ketamine has been associated with several side effects, such as urological complications, sedation, drowsiness, dizziness, and dry mouth (Cvrček, 2008; Storr & Quibell, 2009). Furthermore, high-dose ketamine abuse has been shown to lead to severe bladder disorders, emphasizing the risks of long-term use (Jhang et al., 2018; Y. Li et al., 2021). Consequently, there is growing concern that long-term treatment of depression with ketamine may lead to an increased incidence of bladder problems and lower urinary tract symptoms (Nikayin et al., 2022).

Due to the potential adverse effects and limited data on long-term safety, it is advisable to carefully evaluate the suitability of ketamine treatment for individual patients (Naito et al., 2022). Consequently, the identification of predictive factors for safety, tolerance and effectiveness of ketamine treatment prior to its administration would allow the selection and exclusion of subgroups based on their likelihood of responding positively or negatively to treatment (Iadarola et al. 2015; Rong et al. 2018). Notably, recent studies have demonstrated that traditional models for TRD are not effective in predicting non-response to acute intravenous ketamine treatment, highlighting the need for alternative or revised prediction models (Sakurai et al., 2022). Research has been conducted focusing on genomics and other biomarkers, including BDNF (Haile et al., 2014) and vitamin B12 (Lundin et al., 2014; Permoda-Osip et al., 2013). In addition, Rong et al. (2018) identified several baseline predictors of treatment response, including clinical aspects such as BMI and history of suicide attempts; biochemical markers such as vitamin B12 levels; sleep-related findings, especially abnormal delta sleep ratio; neurochemical factors, including glutamine/glutamate ratio; genetic differences, especially in the BDNF allele; and cognitive functions, including processing speed. Furthermore, psychosocial factors have been associated with treatment response, with personality differences thought to be a significant predictor of treatment efficacy (Dale et al., 2020; Shao & Zhu, 2020). For instance, a meta-analysis has demonstrated that personality traits significantly correlate with treatment outcomes in the management of depression, providing insights into potential facilitators and barriers within the therapeutic process (Bucher et al., 2019). Accordingly, assessing patients' personality traits may help to select and optimize treatment success for depressed patients (Bagby et al., 2008).

Personality traits are not typically included in predictive algorithms in clinical practice, highlighting the need for further research to investigate their modulating influence on affective disorders and their treatments (Balestri et al., 2019). Similarly, there is a notable gap in knowledge regarding how specific personality traits affect ketamine treatment, particularly in relation to anhedonia (Ceban et al., 2021).

Personality Traits

There is increasing evidence that personality plays a crucial role in well-being and is linked to both depression and its treatment outcomes (Bojanowska & Piotrowski, 2021; Kotov et al., 2010; Newton-Howes et al., 2014). In order to gain a deeper insight into the etiology of depression, to identify individuals at risk, and to design effective treatments, it is crucial to have a better understanding of the relationship between personality traits and depression (Klein et al., 2011).

Personality can be defined as a combination of several traits as well as specific trait profiles (Shao & Zhu, 2020). Among the most widely studied personality models is the five-factor model of McCrae and Costa (1989), which includes five broad personality traits: agreeableness (related to politeness and compassion), extraversion (related to sociability and assertiveness), neuroticism (related to stress reactivity, emotional instability, and avoidance), conscientiousness (related to achievement orientation and organisation), and openness to experiences short openness (related to fantasy, creativity, and aesthetic appreciation; Costa & McCrae, 1992; Goldberg, 1990).

Research indicates that primarily three traits from the five-factor model—neuroticism, extraversion and conscientiousness—are related to depression (Hakulinen et al., 2015; Wardenaar et al., 2014). In line with this, a meta-analysis of 175 correlational studies found that while neuroticism has a positive correlation with affective disorders, including MDD, extraversion and conscientiousness have a negative correlation (Kotov et al., 2010). Furthermore, differences in personality may influence how patients respond to treatment, the effectiveness of specific treatment modalities, and the type of treatment offered (Mulder, 2002; Ran et al., 2024). For instance, a study examining the correlation between personality differences and treatment response in depression found that high levels of neuroticism had a negative effect on improvement in depressive symptoms, with the effect varying depending on the type of antidepressant and the level of neuroticism (Naito et al., 2022). Similarly, research by Wardenaar et al. (2014) indicated that individuals characterized by high

neuroticism, low extraversion, and low conscientiousness had a poorer treatment response compared to those with moderate neuroticism, high agreeableness, and high conscientiousness.

While literature consistently reports that depressed patients are high in neuroticism, low in extraversion, and low in conscientiousness, findings regarding the relationship between openness and depression have yielded contradictory results, suggesting that there is little to no relationship between openness and depression (Khoo & Simms, 2018; Kotov et al., 2010). However, in relation to ketamine treatment, Dale et al. (2020) surprisingly showed that only the trait of openness significantly predicted a positive response to TRD. One possible interpretation of this finding is that a trait that is only weakly correlated with a diagnosis of depression may still influence the expression of symptoms, the progression of the disorder and the response to treatment (Cain et al., 2012). Furthermore, research has demonstrated that while there is a minimal association between openness and depression, it was a predictor of anhedonia, indicating a stronger relationship with this specific symptom than with global depression (Khoo & Simms, 2018).

Neurobiologically, openness is linked to the dopaminergic neurotransmitter system, which influences the brain's reward pathways and may contribute to the development of anhedonia (DeYoung, 2013). Additionally, resting state functional connectivity studies have found that networks associated with emotional and executive brain functions can predict openness, particularly those networks modulated by the dopamine system involved in reward, pain processing, and vigilance (Nostro et al., 2018).

Consequently, when considering ketamine as a treatment option for depression, it is crucial to assess the potential impact of the trait of openness on treatment outcomes, particularly in terms of its effects on hedonic experience and overall treatment efficacy.

Impact of Openness on Hedonic Experience

Openness “is best characterized by original, imaginative, broad interests, and daring” (McCrae & Costa, 1987, p. 87). More specifically, openness is considered to measure aspects of personality related to intellectual curiosity, exploration of ideas, values or sensations, appreciation of diversity or the unknown, awareness of feelings, aesthetic sensitivity, and the ability to exercise independent judgement and flexible decision-making (McCrae & Costa, 1983).

As previously mentioned, the relationship between openness and depression is complex, with studies suggesting no direct link (Kotov et al., 2010), yet identifying openness as a predictor of anhedonia (Khoo & Simms, 2018). Similarly, Perkovic and Pechenkov (2023) found that traits predicting anhedonia are distinct from those that predict general depressive symptoms like neuroticism and conscientiousness. Furthermore, in a study examining factors influencing anhedonia within a community sample, a negative correlation was reported between openness and anhedonia in the psychiatric sub-cohort (Tobe et al., 2023). These findings suggest that higher levels of openness may enhance engagement and pleasure in everyday activities as well as novel sensations, thus contributing to increased hedonic capacity (Ely et al., 2021; Fayn et al., 2015; Tobe et al., 2023).

Similar findings have been made in the field of aesthetic experience, with openness being associated with an increased experience of aesthetic emotions, such as feelings of being moved and touched, as well as pleasure when listening to music (Silvia et al., 2015). Further emphasizing this connection, it has been observed that individuals with high levels of openness may be more sensitive to aesthetic emotions, as reflected in their increased experience of chills when exposed to aesthetic stimuli (McCrae, 2007; Nusbaum & Silvia, 2011). Similarly, the study by Colver and El-Alayli (2016) found a positive correlation between openness and aesthetic chills.

Subjective Ketamine Experience

As mentioned above, ketamine can cause various side effects, including dissociation or altered consciousness (Ceban et al., 2021; Glue et al., 2021). Although these side effects are usually short-lived, it is crucial to establish whether the quality of the subjective ketamine experience is associated with or impacts the efficacy of the treatment (Ballard & Zarate, 2020). Results in this area are mixed: Some studies indicate that dissociative side effects are positively correlated with a reduction in depressive symptoms, while others fail to replicate a significant association between ketamine-induced dissociation and its antidepressant effect (Grabski et al., 2020; Luckenbaugh et al., 2014). Notably, most studies have focused on whether overall changes in dissociative symptoms correlate with changes in depressive symptom scores but have not examined whether different subdimensions of dissociation differentially influence treatment efficacy (Niciu et al., 2018). This distinction could be particularly important, as the therapeutic effect could depend on a positive ketamine experience, including a pleasant altered state of consciousness and perception, as well as the

avoidance of anxiety (Aday et al., 2021; Passie et al., 2021). In support of this, Aust et al., (2019) found that non-responders to ketamine infusion reported more anxiety-related experiences during the ketamine experience compared to responders, suggesting the potential impact of ketamine-induced anxiety on the efficacy of ketamine.

Therefore, it is crucial to investigate methods to alleviate or prevent anxiety-related experiences during ketamine infusion. One effective approach could be psychoeducation about the dissociated state, with the objective of reducing negative affect and anxiety and increasing positive affect (Muscat et al., 2021). Additionally, providing a calm and secure setting during treatment could further aid in mitigating anxiety (Bayes et al., 2021). Another crucial consideration is the psychological variability; for example, personality differences could be considered when selecting patients for treatment (Bucher et al., 2019). For instance, Aust and colleagues' (2019) study demonstrated a negative correlation between openness and experiences of anxiety during ketamine infusion, indicating that patients with higher levels of openness may be less prone to anxiety in these settings. In line with this, research on psilocybin has found a correlation between openness and positive effects as well as fewer adverse reactions (Aday et al., 2021). Additionally, research involving psilocybin has indicated that openness plays a crucial role in therapeutic success, potentially influencing a patient’s capacity and willingness to engage with the psilocybin experience (Modlin et al., 2023). Thus, greater openness could enhance the acceptance of novel treatment modalities and alleviate concerns about altered conditions, potentially leading to enhanced therapeutic outcomes (Khoo & Simms, 2018).

Research Objectives and Hypotheses

Pleasure encompasses a broad spectrum of emotional, social, and physical experiences that are fundamental for behavioral motivation and the survival of species, with profound implications when these pleasurable experiences are impaired (Kringelbach, 2005; Kringelbach & Berridge, 2009). Recent evidence underscores the impact of ketamine on neural circuits related to disrupted hedonic experiences (Erdem et al., 2022). Although ketamine treatment exhibits fast-acting pro-hedonic properties, it is not without adverse effects and chronic use can lead to complications such as addiction and urinary tract damage (Le et al., 2022; Nikayin et al., 2022). Consequently, a careful selection of individuals who are likely to benefit therapeutically from ketamine is essential (Dale et al., 2020; Sanacora et al., 2017; Meshkat et al., 2023). Crucially, clinical and biochemical predictors determining

the safety and efficacy of ketamine need to be identified before its administration (Iadarola et al., 2015; Rong et al., 2018). Additionally, recent research highlights the significance of psychosocial variables, including personality traits, in influencing the outcomes of ketamine treatments (Dale et al., 2020; Shao & Zhu, 2020). Given the emerging evidence suggesting that openness significantly predicts anhedonia and elicits a positive response to ketamine treatment (Dale et al., 2020; Khoo & Simms, 2018), this thesis aims to examine the influence of the personality trait openness on complex hedonic responses, its interaction with ketamine, and its influence on the subjective ketamine experience.

The investigation of hedonic response in a healthy population provides a fundamental basis for the examination of the effects of personality, particularly the trait of openness, on hedonic experiences following ketamine administration. This foundational understanding is crucial for future research involving cohorts with depression or anhedonia. Specifically, it lays the groundwork for addressing questions regarding patient selection and identifying individuals who are most likely to be receptive to and benefit from ketamine treatment, thereby advancing the field of personalized medicine and tailored treatment approaches. Based on the available data, the following hypotheses will be tested:

- **H1**: Higher levels of openness are associated with an increased hedonic response.
- **H2**: There is a significant interaction between openness and treatment condition in influencing hedonic response, suggesting that the effect of openness on hedonic response varies depending on whether the condition is ketamine or placebo.
- **H3:** Experienced anxiety during ketamine infusion mediates the relationship between openness and hedonic response.

Method

This thesis forms part of a larger project, entitled “Unraveling the Aesthetic Mind in Anhedonia”. However, in the following section, only those procedures that are pertinent to this thesis will be explained, as a detailed description of the study and its measurement would exceed the scope of this thesis. The primary objective of this within-subject, single-blinded, placebo-controlled, crossover study was to delineate the multifaceted effects of ketamine on brain activation and connectivity, as well as on hedonic experience.

Participants

Participants aged between 18–55 were recruited through various channels, including social media postings (e.g., Facebook groups), internal university recruitment platforms (e.g., Sona Systems), and flyers distributed at public locations such as Vienna General Hospital, the University of Vienna, and supermarkets. Additionally, a newsletter was distributed via the mailing lists of the network of cognitive scientists in Vienna (Vienna CogSciHub). A total of 46 participants (26 female, 20 male) aged between 19 and 37 years were included in the study. Due to incomplete participation or incomplete responses to the questionnaires and tasks used, the final sample size varied between the hypotheses, with 42 subjects included in the first hypothesis and 38 in the second and third hypotheses. Detailed descriptive statistics for each sample set are presented in Table A1 in the Appendix. Participants were required to meet the following inclusion criteria: (1) aged between 18 and 55 years, (2) right-handed, (3) in good general physical and mental health, and (4) non-smoker with no history of alcohol or drug abuse. Exclusion criteria included: (1) presence of metal implants or other contraindications to MRI, (2) current use of medication, (3) severe or chronic physical, neurological, or mental illness, (4) pregnancy or lactation, and (5) prior administration of ketamine. All participants gave written informed consent before their participation in the study. The study protocol was approved by the Ethics Committee of the Medical University of Vienna and AGES. Participants were compensated for their time and had the right to withdraw from the experiment at any time.

Experimental Procedure

Phone Assessment

Following initial contact with the study team, potential participants underwent a phone assessment, which served as a preliminary step in pre-filtering the subjects prior to their invitation to the clinic for further detailed screening. During the phone assessment, participants were informed about the study procedures and then asked a series of questions pertaining to their health, including details of their current medications, past illnesses, psychiatric diagnoses, and previous and current drug use (e.g., alcohol, cannabis, cocaine, psychedelics, ketamine, and opioids). Additionally, participants were screened for MRI contraindications, such as metal implants, piercings, or tattoos. Finally, they were asked to provide their personal details, including their contact details, age, and insurance number. If participants met the requisite criteria, an appointment was scheduled for a more

comprehensive screening. Participants were also provided with a detailed document outlining the musical task and the specific criteria for selecting their personal songs for the task.

Screening

During the screening process, a comprehensive medical history was obtained, including a clinical psychiatric assessment, a routine physical examination (e.g., weight measurement, blood tests, and medical history review), and a drug screening. In addition to the standard diagnostic tests, psychological scales were administered. The following questionnaires were used during the screening and served as a baseline: the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Beck Depression Inventory (BDI) to measure depressive symptoms. The Barcelona Music Reward Questionnaire (BMRQ) was utilized to comprehend the degree of reward sensitivity towards music, the Aesthetic Experiences Scale (AES) was employed to assess aesthetic experiences, and the NEO-Five-Factory Inventory (NEO-FFI) was employed to document personality traits. Regarding anhedonia and the dimensions of pleasure, the Dimensional Anhedonia Rating Scale (DARS), the Temporal Experience of Pleasure Scale (TEPS), and the Music Task were presented. In accordance with the inclusion and exclusion criteria, participants who fulfilled the criteria were enrolled into the study.

MRI Scanning Sessions

The MRI sessions comprised two treatment days, with subjects receiving ketamine on one day and a placebo on the other. These sessions are single-blinded and randomized, with a minimum interval of two weeks between sessions to reduce the likelihood of carry-over effects.

Following the initial weight check and urine drug test, participants completed some questionnaires, including the MADRS, BDI, and DARS, along with task instructions for the MRI. To ensure comprehension of the instructions, participants were also asked task-related questions, such as "What does the aesthetic scale measure?" Throughout the day, blood samples were collected at regular intervals, and blood pressure was monitored. Approximately 60 minutes into the study, the study drug (ketamine or placebo) was administered over a 40-minute period. Post-administration, participants completed two additional questionnaires: the Visual Analogue Scale (VAS) to assess health status and the 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) to evaluate altered states of consciousness. Following a 60-minute observation period (during which participants

remained in the designated room), they took a lunch break, ensuring that no caffeinated beverages were consumed. Shortly before the scanner tasks, participants completed the VAS and the DARS again. Based on previous research by Mkrtchian et al. (2021) in healthy participants, which showed that hedonic responses increased 230 minutes after ketamine administration, testing in the scanner began four hours after administration of the study drug. The tasks in the scanner were conducted in the following order: music task, money reward task, and sexual arousal task. Additionally, physiological data, specifically respiratory rate, was recorded during these tasks. Subsequently, the MADRS and BDI were administered once more, in addition to two empathy tasks. Following a final examination by the study doctor and a self-assessment of whether the participants believed they had received ketamine or placebo; the participants were discharged.

End-of-Study Examination

The end-of-study examination was conducted within two weeks of the final scanning session. The examinations included a routine physical examination, as performed at the screening visit, which included a blood sample and drug screening. At this visit, the music task was also performed again, and the participants completed a series of psychological questionnaires. The following questionnaires were conducted: MADRS, DARS, AES, BMRQ, BDI and NEO-FFI. Should a subject cease participation in the study, they were still required to undergo a final examination, during which the reasons for their withdrawal or discontinuation were recorded in detail. Furthermore, all adverse events that occurred during the study were recorded.

Study Drug

In the ketamine condition, a dose of 0.5mg per kg body weight of racemic ketamine (comprising the optical enantiomers R-ketamine and S-ketamine) was administered following established protocols and clinical guidelines. In the placebo condition, a saline solution was administered.

Tasks and Measures

Musik Task

The music task was designed based on literature by Salimpoor et al. (2009) with the objective of eliciting hedonic experiences in participants. For this purpose, participants were

required to identify 10 pieces of music that elicited strong positive emotions, such as pleasure, and were thus aesthetically moving to them. Additionally, they were asked to name 10 neutral pieces of music that they found minimally or not aesthetically moving. After an initial sample song to test the volume and familiarize themselves with the scanner, participants listened to their self-selected positive and neutral songs in a randomized order. Each song was played for 70 seconds, after which participants answered the following questions in sequence: "Were you aesthetically moved?", "Did you feel a pleasant chill?", and "How pleasant or unpleasant was the experience for you?". Responses were measured on a 10-point scale, with the first two questions ranging from 1 (*not at all*) to 10 (*as much as possible*) and the third question ranging from -5 (*as unpleasant as possible*) to 5 (*as pleasant as possible*). In this analysis, the question of whether the participant was aesthetically moved is used as an indicator of a complex hedonic response. To avoid bias from the somewhat unpleasant MRI environment the data from the screening session (hereafter referred as baseline dataset) will be used for the first hypothesis to analyze the general relationship between openness and hedonic response. For the second and third hypotheses, the data from the scanning sessions (hereafter referred as treatment dataset) will be used to assess the effects of ketamine. This analysis will use the positive songs only, as they have already been perceived as pleasurable in the past and are therefore expected to elicit stronger hedonic responses.

NEO Five-Factor Inventory (NEO-FFI)

The NEO-FFI (Costa & McCrae, 1992) is a multidimensional personality inventory used to assess the most important areas of individual differences. For the present study, the German version was utilized (Borkenau & Ostendorf, 2008). The NEO-FFI consists of five subscales with a total of 60 items, measuring the following five dimensions: (1) neuroticism, (2) extraversion, (3) openness, (4) agreeableness, and (5) conscientiousness. This analysis focused on the openness subscale, which was surveyed in the screening. The subscale comprises 12 items and is designed to measure the willingness to engage with new experiences, ideas, and values on a 5-point scale (from 0 = *strongly disagree* to 4 = *strongly agree*).

5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)

The German version of 5D-ASC rating scale (Dittrich, 1998) was employed to evaluate subjective effects and alterations from usual waking consciousness during ketamine infusion. The questionnaire comprises 94 items, which assess five key dimensions of altered states of consciousness: (1) oceanic boundlessness, (2) dread of ego disolution, (3) visionary restructuralization, (4) auditory alterations, and (5) reduction of vigilance. A more recent approach, proposed by Studerus et al. (2010), suggests the use of eleven lower-order subscales: (1) experience of unity, (2) spiritual experience, (3) blissful state, (4) insightfulness,(5) disembodiment, (6) impaired control and cognition, (7) anxiety, (8) complex imagery, (9) elementary imagery, (10) audio-visual synesthesia, and (11) changed meaning of percepts. The dimension "dread of ego dissolution" assesses phenomena associated with a bad trip, including loss of self-control, thought disorder, agitation, and anxiety. Of particular significance within this dimension is the subscale designated as "anxiety". This subscale will be employed in the subsequent analysis. The anxiety subscale comprises six items, which are used to measure anxiety during the ketamine infusion on a visual scale from 0 to 100 (0 = *no, not more than usual* to 100 = *yes, much more than usual*).

Statistical Analysis

Microsoft Excel for Windows (Version 2405; Microsoft Corporation, 2018) was used for data preparation, where corresponding items were recoded, and subscale sum values were calculated for each participant. Subsequent statistical analyses were conducted using R version 4.4.4 (R Core Team, 2021) within the RStudio environment (RStudio Team, 2020). Descriptive statistics, including means and standard deviations, were derived for the openness subscale, with separate computations for the baseline and treatment datasets due to the different sample sizes between the two datasets. In addition, means and standard deviations were calculated for the anxiety subscale in both ketamine and placebo conditions, and for the hedonic response question in the music task in baseline, ketamine and placebo conditions (see Table A2 in the appendix for detailed variable descriptions for each dataset).

To test the first hypothesis—whether higher levels of openness are associated with increased hedonic responses—a linear mixed-effects model was performed using the data from the screening (baseline dataset). Initially, two linear mixed-effects models with increasing levels of complexity were fitted to determine the most appropriate model: (1) a model that included openness as a predictor and accounted for individual differences in

baseline hedonic response (participants as random intercept), and (2) a model that added random slopes for openness in addition to the random intercept, allowing the effect of openness to vary across individuals. These models were compared using analysis of variance (ANOVA) and Akaike information criteria (AIC), as wells as Bayesian information criteria (BIC) to identify the best-fitting model. Based on these comparisons, the first model including openness as a fixed effect and participants as a random intercept was selected as the most appropriate due to its balance between goodness-of-fit and parsimony. The model specification was as follows: Hedonic response ~ Openness + (1 | Participants).

To test the second hypothesis—whether there is an interaction between openness and treatment condition (placebo vs. ketamine) in influencing hedonic responses—another linear mixed-effects model was employed using the data from the two scanning sessions (treatment dataset). This model extended the initial model by including the treatment condition and treatment order as a fixed effects and an interaction term between openness and condition. Four models with different random effect structures were fitted to determine the most suitable model: (1) a model with a random intercept to account for individual differences, (2) a model that added random slopes for openness, allowing the effect of openness to vary across individuals, (3) a model that added random slopes for the treatment condition, allowing the effect of the treatment condition to vary across individuals, and (4) a model that included random slopes for both openness and the treatment condition. These models were also compared using ANOVA and information criteria (AIC and BIC), with the random slopes model for the treatment conditions (Model 3) ultimately identified as the optimal fitting model. The model specification was as follows: Hedonic response ~ Openness * Condition + Treatment Order + (1 + Condition | Participants) with ketamine as the reference category for the treatment condition. Both models were fitted using the "lmer" function from the "lme4" package and maximum likelihood estimation (Bates et al., 2015).

To test the third hypothesis—whether anxiety mediates the relationship between openness and hedonic responses—a mediation model was employed using the "process" function from the "bruceR" package (Bao, 2024). This model assessed openness as the independent variable, anxiety as the mediator, and hedonic response as the dependent variable. For this analysis, data exclusively from the ketamine condition were used, as it specifically pertains to anxiety during ketamine infusion.

Following model selection, diagnostic checks validated the assumptions of the linear mixed-effects models and the mediation model. Some assumptions, such as linearity, homoscedasticity, and the absence of outliers, were not fully met in both types of models.

Although further steps such as variable transformation or robust statistical methods could address these issues, they were beyond the scope of this thesis. Consequently, the results should be interpreted with caution. Given the limited sample size and the low variability of the openness scores, caution should be exercised in interpreting the results, as the statistical power may be relatively low. The significance level was set at $p < 0.05$.

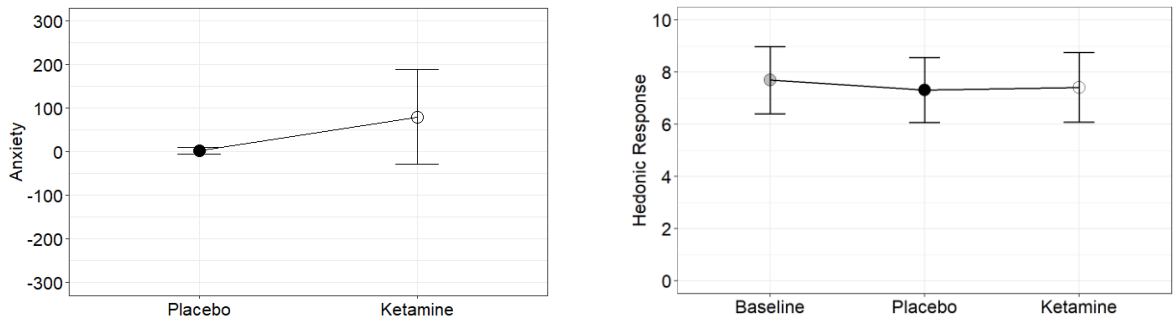
Results

Descriptive Data

The mean score for openness was 35.81 (*SD* = 4.92) in the baseline dataset and 36.79 (*SD* = 4.29) in the treatment dataset. Anxiety scores during the placebo condition had a mean of 2.24 (*SD* = 8.12), while during the ketamine condition, the mean anxiety score was 80.53 (*SD* = 109.24). Hedonic response scores showed a mean of 7.69 (*SD* = 1.30) at baseline, 7.32 (*SD* = 1.25) in the placebo condition and 7.42 (*SD* = 1.34) in the ketamine condition (see Figure 1).

Figure 1

Means and Standard Deviations for Anxiety and Hedonic Response



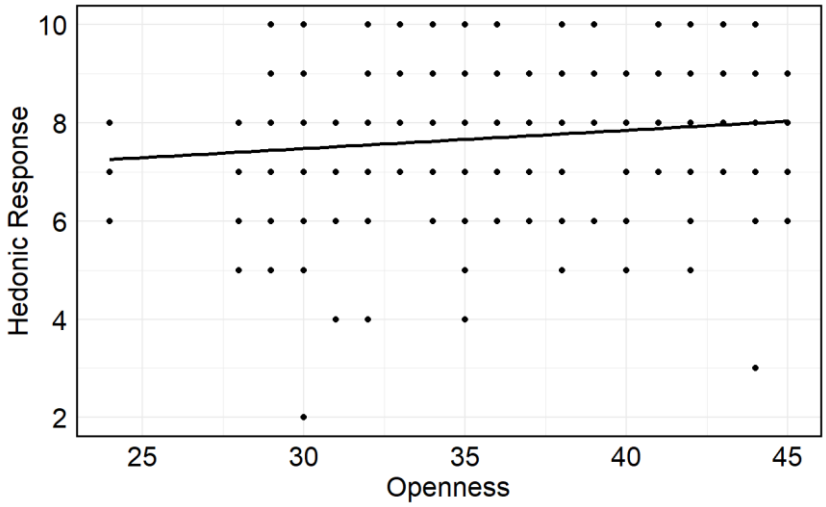
Note. For anxiety, the high variance of the scores means that the error bars extend into negative values, even though the scale is 0-100.

Effect of Openness on Hedonic Response

The results of the linear mixed-effects model, including openness as an independent variable and accounting for individual differences in hedonic response (participant as a random intercept), showed that the fixed effect of openness on hedonic response was marginal and not statistically significant, $B = 0.04$, $SE = 0.03$, 95% CI [-0.02, 0.09], $t(42.04) = 1.36$, $p = .180$ (see Figure 2). The relationship between openness and hedonic response showed a variance in intercepts across participants, Var(u0j) = 0.67.

Figure 2

Effect of Openness on Hedonic Response



Note. $n = 42$.

Interaction between Openness and Treatment Condition

The results of the linear mixed-effects model, including openness, treatment condition (ketamine vs. placebo), treatment order, and the interaction between openness and treatment condition as fixed effects and accounting for individual differences in hedonic response (participant as random intercept and random slope for treatment condition), are shown in Table 1. There was no significant main effect of openness, treatment condition, treatment order, or the interaction between openness and treatment condition. There was variance in the intercepts (Var(u0j) = 0.75), indicating variability in the hedonic response between participants. There was also variance in the slopes for treatment condition (Var(u1j) = 0.26), indicating that the effect of treatment condition on hedonic response varied across participants.

Table 1

Interaction Effect between Openness and Treatment Condition

			95% CI				
	Estimate	*SE*	Lower	Upper	df	*t*-value	*p*-value
Intercept	7.61	1.3	4.89	10.33	36.63	5.80	<.001
Openness	-0.00	0.04	-0.07	0.07	36.60	-0.05	.958
Condition	-1.15	0.97	-3.05	0.74	37.44	-1.19	.240
Order	-0.30	0.26	-0.81	0.20	38.08	-1.17	.248
Openness*Condition	0.03	0.03	-0.02	0.08	37.47	1.10	.277

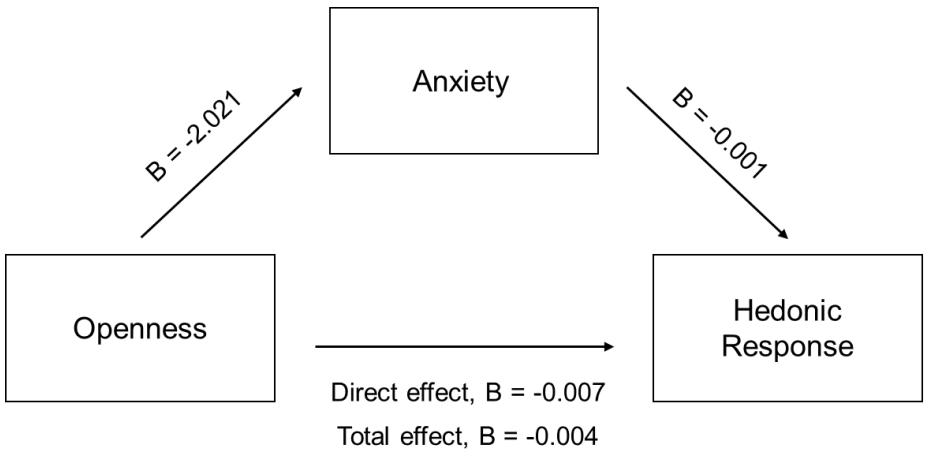
Note. $n = 38$. Ketamine is the reference category for the treatment condition.

Mediating Effect of Anxiety

A mediation model was conducted to analyze the mediating role of anxiety in the relationship between openness and hedonic response (see Figure 3). The initial effect of openness on hedonic response was not significant ($B = -0.007$, $p = .863$). When anxiety was included in the model as mediator, openness did not significantly predict anxiety ($B = -2.021$, $p = .636$), and anxiety did not significantly predict hedonic response ($B = -0.001$, $p=.377$). The indirect effect of openness on hedonic response through anxiety was not significant ($B = 0.003$, 95% CI [-0.008, 0.035], $p = .783$). Consequently, the total effect of openness on hedonic response remained non-significant, ($B = -0.004$, $p = .914$).

Figure 3

Mediating Effect of Anxiety



Note. n = 38. Confidence interval for the indirect effect is a Bias-Corrected and Accelerated bootstrapped CI based on 1000 samples.

Discussion

In terms of the overall research aim of this thesis, which is to advance the field of personalized medicine and the identification of those individuals who are most likely to benefit from ketamine treatment, the results of this thesis provide initial insights. This thesis attempts to investigate the influence of personality on the hedonic effects of ketamine. In particular, the following three hypotheses were tested: (1) higher levels of openness are associated with a greater hedonic response; (2) there is a significant interaction between openness and treatment condition in influencing hedonic response; (3) experienced anxiety during ketamine infusion mediates the relationship between openness and hedonic response.

In sum, none of the formulated hypotheses yielded a statistically significant result. However, it should be noted that the study was not originally designed with the intent to investigate the effects of personality traits. Furthermore, caution is required when interpreting the results, as the mean value of the personality trait openness was high (baseline dataset: M = 35.81; treatment dataset: M = 36.79) and the standard deviation was low (baseline dataset: SD = 4.92; treatment dataset: SD = 4.29). In comparison, the mean level of openness in the NEO-FFI manual (n = 11.724) was 32.10, with a standard deviation of 6.48 (Borkenau & Ostendorf, 2008). This suggests that the study group used for this analysis showed a high degree of homogeneity in terms of openness, with scores above the average. Previous

research has demonstrated that personality traits can influence an individual's willingness to participate in clinical trials, potentially leading to self-selection bias (Almeida et al., 2008; Gouveia et al., 2022). Given this, the results are biased by the lack of variation and may result in low statistical power, making it not possible to draw meaningful conclusions. However, patients with depression are likely to exhibit lower and more variable scores on the openness scale, which may be associated with the heterogeneity and severity of their symptoms, including anhedonia (Klein et al., 2011). Indeed, research has demonstrated a negative correlation between openness and the severity of anhedonia (Tobe et al., 2023). These findings are consistent with the idea that higher levels of openness are associated with greater engagement in daily activities, potentially reflecting a greater capacity to experience pleasure (Fayn et al., 2015; Tobe et al., 2023). Due to the limitations imposed by the homogeneity of openness, the focus of this discussion is less on the statistical significance of the results, but rather on the direction of the observed effects and suggestions for improvement for future studies in order to obtain more robust and meaningful results.

The effect of the first hypothesis points in the right direction, suggesting that greater openness may lead to stronger hedonic responses. However, it should not be overlooked that the effect is very small or barely present. Reasons for this, apart from the above mentioned, could be that different facets of openness have varying impacts on hedonic experiences. For example, Khoo et al. (2018) showed that while openness accounted for a significant proportion of anhedonia, at the facet level only the value facet (representing the re-examination of personal values and the values of authority figures) contributed significant unique variance to the prediction of anhedonia. Similar findings have been reported for aesthetic emotions. Using an alternative model of openness with two facets (openness and intellect), it was found that only openness and not intellect was a predictor of increased arousal, interest, and pleasure (Fayn et al., 2015).

While the second hypothesis assumed that there would be an interaction between openness and treatment condition affecting hedonic response, the data did not confirm this assumption. This indicates that the effect of openness on hedonic response does not vary depending on whether the condition is ketamine or placebo. However, these results should be treated with caution, as this is the first time that the influence of openness on hedonic experience has been investigated in the context of ketamine, rather than depression in general (Dale et al., 2020). The direction of the main effect of treatment condition suggests that ketamine had a more positive effect on hedonic response compared to placebo. These findings are in contrast to another study, which showed that ketamine tended to increase

anhedonia in healthy participants within the first 24 hours after infusion (Nugent et al., 2019). However, it should be noted that the study used questionnaires to measure anhedonia, which are not appropriate for measuring changes in hedonic response in healthy participants. In addition, the measurements in that study were taken earlier (at 40, 80, 120, and 230 minutes post-infusion) compared to the present study (240 minutes post-infusion). Previous research by Mkrtchian et al. (2021) observed that healthy participants exhibited an initial decrease in hedonic experience after ketamine administration, which then improved after 230 minutes, underscoring the importance of the timing of hedonic response assessment. Overall, this discrepancy highlights the existing inconsistency of research findings on hedonic response in healthy participants following ketamine treatment and the methodological challenges associated with investigating hedonic responses to ketamine.

Contrary to the third hypothesis, anxiety does not mediate the relationship between openness and hedonic response, exhibiting only minimal to negligible effects. However, looking at the directions of the individual effects in the mediation analysis, openness is negatively correlated with anxiety. This finding aligns with previous research showing a negative correlation between openness and adverse effects, including anxiety, during treatments with ketamine or psilocybin (Aday et al., 2021; Aust et al., 2019; Smigielski et al., 2019). Furthermore, the mediation analysis reveals that anxiety has a negative effect on the hedonic response. However, this effect is only very minimal to barely present, indicating that variations in anxiety levels have a relatively limited impact on hedonic response at 240 min post-infusion. This contrasts with the results of Aust et al. (2019) who showed that anxiety during ketamine infusion had an impact on antidepressant efficacy. However, the study only looked at the effects on depression symptoms in general and not specifically on anhedonia or hedonic responses. The impact of induced anxiety may vary between healthy participants and patients with anhedonia, as pre-existing symptoms of depression may influence the effect of anxiety on treatment outcomes (Gaspersz et al., 2018). For example, increased baseline anxiety and restlessness may make patients more susceptible for anxious experiences during the treatment and negative effects of anxiety on the overall treatment experience, including hedonic experiences (Breeksema et al., 2022). Furthermore, restricted psychological flexibility may impair the capacity to adapt to treatment-related uncertainty and unpredictability (Breeksema et al., 2022; Davis et al., 2020). This inability to effectively manage uncertainty and experienced anxiety may prolong and exacerbate anxiety and affect treatment outcomes (Davis et al., 2020). Conversely, healthy subjects with more resilient emotional processing and psychological flexibility may be better able to cope with ketamine-

induced anxiety, resulting in less impact of the experienced anxiety on treatment outcome (Rademacher et al., 2023).

Limitations

Following on from the previous paragraph, some limitations of the study need to be mentioned. The first limitations relate to the sample. The sample is not only limited in size but also homogeneous, compromising approximately 79% students with an average age of approximately 24. This demographic bias results in a predominantly WEIRD (Western, Educated, Industrialized, Rich, and Democratic) sample (Alley & Cortina, 2023). Such a limitation is important because most psychological studies rely on WEIRD samples, which are not representative of the global population (Rad et al., 2018). Consequently, the findings obtained from such samples may not be generalizable. Furthermore, it is possible that participants did not provide accurate information about some of the inclusion and exclusion criteria for the study. For instance, although the drug test indicated that the participants were not currently using drugs, it cannot be ruled out that they may have misreported their past drug use, particularly ketamine, which could influence the data.

Secondly, there are also some procedural and study design limitations. One notable limitation was the use of a saline solution as a placebo, which did not control for the potential non-therapeutic effects of ketamine, such as altered mental and physiological states. The psychoactive effects of ketamine often unblinded participants, allowing them to recognize whether they were receiving ketamine or the placebo (Wilkinson et al., 2019). Indeed, 86.84% of participants correctly identified their treatment condition in both sessions. It is possible that recognition of the treatment administered may influence subjective judgments and lead to an overestimation of the therapeutic effect (Bloomfield-Clagett et al., 2022). In the context of this thesis, treatment recognition may lead to a subject-expectancy effect, which may have influenced self-reported hedonic experience during the music task (Lii et al., 2023). However, given that the subject-expectancy effect is more likely to result in an overestimation of the effects of ketamine (Aday et al., 2021; Muthukumaraswamy et al., 2021) and that the treatment condition was not significant in the linear mixed model (which suggests that there was not a large difference in hedonic responses between ketamine and placebo), it is unlikely that treatment recognition biased the results to the extent that they became non-significant. Nevertheless, establishing an appropriate control condition to effectively assess the rapid antidepressant and pro-hedonic effects of ketamine remains a

significant challenge that requires careful consideration (Laursen et al., 2023). One way to overcome this problem and maintain blinding is by using an active placebo control (Fitzgerald et al., 2021). Midazolam, a short-acting benzodiazepine, is often used as an active placebo in ketamine studies because its sedative effect produces a similar subjective experience to ketamine without its therapeutic benefit (Adhikari et al., 2020; Dwyer et al., 2021). Despite the frequent use of midazolam as an active placebo in ketamine trials to maintain blinding, the acute dissociative and psychomimetic effects of ketamine may still reveal to participants which investigational drug they have received (Dwyer et al., 2021; Shiroma et al., 2020). Another limitation is that the duration of each study session was very long, and several participants reported significant fatigue and exhaustion after the MRI tasks. Consequently, the long duration of the study day, combined with the conditions of the music task—specifically, lying within an MRI scanner amidst loud noises—may have influenced the participants' hedonic experience. As such, possible differences in hedonic response that might arise from openness, or the treatment condition could have been muted if participants were too fatigued or uncomfortable to fully engage with the music task. Furthermore, self-selected pieces of music were used for the music task, as research has shown that these elicit the strongest hedonic response (Zatorre, 2015). However, there are limitations to this approach. Specifically, we did not control for familiarity or the frequency with which participants listened to the songs before and between sessions, even though familiarity and repeated exposure to music are important factors in modulating emotional and hedonic experiences (Freitas et al., 2018; Verhaeghen, 2018). Accordingly, repeated exposure not only increases familiarity with the music, but also increases positive feelings, referred to as the "mere-exposure effect" (Zajonc, 1986). Because we used self-selected music, participants were already familiar with the music, so repeated exposure to the music probably did not result in significant changes in hedonic experience. However, research has shown that the relationship between exposure and enjoyment is not linear, but rather follows an inverted U-shape, with increased familiarity initially leading to more pleasure but eventually to increased displeasure (Chmiel & Schubert, 2017; Szpunar et al., 2004). Consequently, increased listening between the two MRI sessions could potentially shift the position on the inverted U-curve. However, because we randomized the order of ketamine and placebo between sessions, systematic order effects should have been minimized.

Implications for Future Research

As the study was not originally designed to investigate the effect of openness on hedonic response, there are some aspects of the design of the study that are not appropriate for investigating the hypotheses of this thesis. Consequently, there is a need for further research with a more suitable design.

As mentioned above, the sample had a high mean score of openness with a low variance and was very homogeneous with many students. A previous study by Brisson & Bianchi (2022) showed that different levels of openness were found depending on the level of education, with people with higher levels of education showing higher levels of openness. Furthermore, there is evidence that age may have an impact on openness, suggesting a negative correlation between the two variables (Donnellan & Lucas, 2008). Therefore, as a first step for further studies, it would be important to recruit a diverse sample with different educational backgrounds and age groups and match them to patients with anhedonia.

In order to gain deeper insights into the relationship between openness and hedonic experience, it would be important to analyze the influence of the facet levels of openness, rather than focusing solely on the domain level of openness. Furthermore, the use of diverse models of openness would be crucial, as different models are characterized by their unique qualitative and quantitative facet structures (Khoo & Simms, 2018). For example, DeYoung et al. (2012) proposed a new structure of the openness trait, including openness and intellect, with positive schizotypy being associated with openness and intelligence with intellect. Conversely, Soto and John (2017) conceptualize openness in their model as open-mindedness, comprising three dimensions: intellectual curiosity, aesthetic sensitivity, and creative imagination. Future studies should examine the facet-level relationship between openness and hedonic experience, and subsequently apply alternative models of openness.

Conclusion

In conclusion, although the study as a whole was not primarily designed to investigate the influence of openness on the hedonic experience and its interaction with ketamine, the direction of the results provides first hints regarding the importance of personality on the hedonic response following ketamine administration. This thesis has identified key aspects that should be considered in future studies to gain a deeper understanding of the influence of personality traits on the efficacy of ketamine treatment and to advance the field of personalized medicine by identifying appropriate predictors of treatment. Ultimately, this

could lead to improved individualized treatment approaches in clinical practice and optimized therapeutic outcomes.

References

Acevedo-Diaz, E. E., Cavanaugh, G. W., Greenstein, D., Kraus, C., Kadriu, B., Zarate, C. A., & Park, L. T. (2020). Comprehensive assessment of side effects associated with a single dose of ketamine in treatment-resistant depression. *Journal of Affective Disorders*, *263*, 568–575. https://doi.org/10.1016/j.jad.2019.11.028

Aday, J. S., Davis, A. K., Mitzkovitz, C. M., Bloesch, E. K., & Davoli, C. C. (2021). Predicting reactions to psychedelic drugs: A systematic review of states and traits related to acute drug effects. *ACS Pharmacology & Translational Science*, *4*(2), 424–435. https://doi.org/10.1021/acsptsci.1c00014

Adhikari, B. M., Dukart, J., Hipp, J. F., Forsyth, A., McMillan, R., Muthukumaraswamy, S. D., Ryan, M. C., Hong, L. E., Eickhoff, S. B., Jahandshad, N., Thompson, P. M., Rowland, L. M., & Kochunov, P. (2020). Effects of ketamine and midazolam on resting state connectivity and comparison with ENIGMA connectivity deficit patterns in schizophrenia. *Human Brain Mapping*, *41*(3), 767–778. https://doi.org/10.1002/hbm.24838

Aleksandrova, L. R., & Phillips, A. G. (2021). Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. Trends in Pharmacological Sciences, 42(11), 929–942. https://doi.org/10.1016/j.tips.2021.08.003

Automatische Updates der Zitationen sind deaktiviert. Um das Literaturverzeichnis anzuzeigen, klicken Sie auf Aktualisieren im Zotero-Reiter.Almeida, L., Kashdan, T. B., Nunes, T., Coelho, R., Albino-Teixeira, A., & Soares-da-Silva, P. (2008). Who volunteers for phase I clinical trials? Influences of anxiety, social anxiety and depressive symptoms on self-selection and the reporting of adverse events. *European Journal of Clinical Pharmacology, 64*(6), 575–582. https://doi.org/10.1007/s00228-008-0468-8

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., de Girolamo, G., de Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J. M., Katz, S. J., Kessler, R. C., Kovess, V., Lépine, J. P., Ormel, J., Polidori, G., Russo, L. J., … Vollebergh, W. A. M. (2004). Disability and quality of life impact of mental disorders in Europe: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica*, *109*(420), 38–46. https://doi.org/10.1111/j.1600-0047.2004.00329.x

American Psychiatric Association. (2015). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Armour, C., Tsai, J., Durham, T. A., Charak, R., Biehn, T. L., Elhai, J. D., & Pietrzak, R. H. (2015). Dimensional structure of DSM-5 posttraumatic stress symptoms: Support for a hybrid anhedonia and externalizing behaviors model. *Journal of Psychiatric Research*, *61*, 106–113. https://doi.org/10.1016/j.jpsychires.2014.10.012

Aust, S., Gärtner, M., Basso, L., Otte, C., Wingenfeld, K., Chae, W. R., Heuser-Collier, I., Regen, F., Cosma, N. C., Van Hall, F., Grimm, S., & Bajbouj, M. (2019). Anxiety during ketamine infusions is associated with negative treatment responses in major depressive disorder. *European Neuropsychopharmacology*, *29*(4), 529–538. https://doi.org/10.1016/j.euroneuro.2019.02.005

Bagby, R. M., Quilty, L. C., Segal, Z. V., McBride, C. C., Kennedy, S. H., & Costa, P. T. (2008). Personality and differential treatment response in major depression: A randomized controlled trial comparing cognitive-behavioural therapy and pharmacotherapy. *Canadian journal of psychiatry. Revue canadienne de psychiatrie*, *53*(6), 361–370. https://doi.org/10.1177/070674370805300605

Balestri, M., Porcelli, S., Souery, D., Kasper, S., Dikeos, D., Ferentinos, P., Papadimitriou, G. N., Rujescu, D., Martinotti, G., Di Nicola, M., Janiri, L., Caletti, E., Mandolini, G. M., Pigoni, A., Paoli, R. A., Lazzaretti, M., Brambilla, P., Sala, M., Abbiati, V., … Serretti, A. (2019). Temperament and character influence on depression treatment outcome. *Journal of Affective Disorders*, *252*, 464–474. https://doi.org/10.1016/j.jad.2019.04.031

Ballard, E. D., & Zarate, C. A. (2020). The role of dissociation in ketamine's antidepressant effects. *Nature Communications*, *11*(1), 6431. https://doi.org/10.1038/s41467-020-20190-4

Bao, H. W. S. (2021). *bruceR: Broadly useful convenient and efficient R functions*. https://CRAN.R-project.org/package=bruceR

Bates, D., Mächler M., Bolker B., & Walker, S. (2015). "Fitting Linear Mixed-Effects Models Using lme4." *Journal of Statistical Software*, 67(1), 1–48. https://doi:10.18637/jss.v067.i01.

Bayes, A., Dong, V., Martin, D., Alonzo, A., Kabourakis, M., & Loo, C. (2021). Ketamine treatment for depression: A model of care. *Australian & New Zealand Journal of Psychiatry*, *55*(12), 1134–1143. https://doi.org/10.1177/00048674211039166

Berlin, I., Givry-Steiner, L., Lecrubier, Y., & Puech, A. J. (1998). Measures of anhedonia and hedonic responses to sucrose in depressive and schizophrenic patients in comparison with healthy subjects. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *13*(6), 303–309. https://doi.org/10.1016/S0924-9338(98)80048-5

Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry*, *47*(4), 351–354. https://doi.org/10.1016/S0006-3223(99)00230-9

Berridge, K. C. (2003). Pleasures of the brain. *Brain and Cognition*, *52*(1), 106–128. https://doi.org/10.1016/s0278-2626(03)00014-9

Berridge, K. C., & Kringelbach, M. L. (2008). Affective neuroscience of pleasure: Reward in humans and animals. *Psychopharmacology*, *199*(3), 457–480. https://doi.org/10.1007/s00213-008-1099-6

Berridge, K. C., & Kringelbach, M. L. (2011). Building a neuroscience of pleasure and well-being. *Psychology of well-being*, *1*(1), 1–3. https://doi.org/10.1186/2211-1522-1-3

Berridge, K. C., & Kringelbach, M. L. (2015). Pleasure Systems in the Brain. *Neuron*, *86*(3), 646–664. https://doi.org/10.1016/j.neuron.2015.02.018

Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences*, *26*(9), 507–513. https://doi.org/10.1016/S0166-2236(03)00233-9

Berridge, K. C., & Robinson, T. E. (2016). Liking, wanting, and the incentive-sensitization theory of addiction. *American Psychologist*, *71*(8), 670–679. https://doi.org/10.1037/amp0000059

Berridge, K. C., Robinson, T. E., & Aldridge, J. W. (2009). Dissecting components of reward: 'Liking', 'wanting', and learning. *Current Opinion in Pharmacology*, *9*(1), 65–73. https://doi.org/10.1016/j.coph.2008.12.014

Bignardi, G., Chamberlain, R., Kevenaar, S. T., Tamimy, Z., & Boomsma, D. I. (2022). On the etiology of aesthetic chills: A behavioral genetic study. *Scientific Reports*, *12*(1), 3247. https://doi.org/10.1038/s41598-022-07161-z

Blood, A. J., & Zatorre, R. J. (2001). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(20), 11818–11823. https://doi.org/10.1073/pnas.191355898

Bloomfield-Clagett, B., Ballard, E. D., Greenstein, D. K., Wilkinson, S. T., Grunebaum, M. F., Murrough, J. W., Mathew, S. J., Phillips, J. L., Fava, M., Sanacora, G., & Zarate, C. A., Jr. (2022). A participant-level integrative data analysis of differential placebo response for suicidal ideation and nonsuicidal depressive symptoms in clinical trials of intravenous racemic ketamine. *International Journal of Neuropsychopharmacology, 25*(10), 827–838. https://doi.org/10.1093/ijnp/pyac055

Bojanowska, A., & Piotrowski, K. (2021). Two levels of personality: Temperament and values and their effects on hedonic and eudaimonic well-being. *Current Psychology*, *40*(3), 1185–1193. https://doi.org/10.1007/s12144-018-0043-0

Borkenau, P., & Ostendorf, F. (2008).*NEO-FFI : NEO-Fünf-Faktoren-Inventar nach Costa und McCrae, Manual* (2nd ed.). Hogrefe.

Borsini, A., Wallis, A. S. J., Zunszain, P., Pariante, C. M., & Kempton, M. J. (2020). Characterizing anhedonia: A systematic review of neuroimaging across the subtypes of reward processing deficits in depression. *Cognitive, Affective, & Behavioral Neuroscience*, *20*(4), 816–841. https://doi.org/10.3758/s13415-020-00804-6

Boyer, P., Tassin, J. P., Falissart, B., & Troy, S. (2000). Sequential improvement of anxiety, depression and anhedonia with sertraline treatment in patients with major depression. *Journal of Clinical Pharmacy and Therapeutics*, *25*(5), 363–371. https://doi.org/10.1111/j.1365-2710.2000.00302.x

Brattico, E., Bogert, B., & Jacobsen, T. (2013). Toward a Neural Chronometry for the Aesthetic Experience of Music. *Frontiers in Psychology*, *4*, 206. https://www.frontiersin.org/journals/psychology/articles/10.3389/fpsyg.2013.00206

Breeksema, J. J., Niemeijer, A., Krediet, E., Karsten, T., Kamphuis, J., Vermetten, E., van den Brink, W., & Schoevers, R. (2024). Patient perspectives and experiences with psilocybin treatment for treatment-resistant depression: A qualitative study. *Scientific Reports, 14*(1), 2929. https://doi.org/10.1038/s41598-024-53188-9

Brisson, R., & Bianchi, R. (2022). Aesthetic disposition, educational capital, personality trait openness, and sex: A study of French high-school students. *Empirical Studies of the Arts, 40*(2), 259–274. https://doi.org/10.1177/02762374211047973

Bucher, M. A., Suzuki, T., & Samuel, D. B. (2019). A meta-analytic review of personality traits and their associations with mental health treatment outcomes. *Clinical Psychology Review*, *70*, 51–63. https://doi.org/10.1016/j.cpr.2019.04.002

Cain, N. M., Ansell, E. B., Wright, A. G. C., Hopwood, C. J., Thomas, K. M., Pinto, A., Markowitz, J. C., Sanislow, C. A., Zanarini, M. C., Shea, M. T., Morey, L. C.,

McGlashan, T. H., Skodol, A. E., & Grilo, C. M. (2012). Interpersonal pathoplasticity in the course of major depression. *Journal of Consulting and Clinical Psychology, 80*(1), 78–86. https://doi.org/10.1037/a0026433

Cao, B., Park, C., Subramaniapillai, M., Lee, Y., Iacobucci, M., Mansur, R. B., Zuckerman, H., Phan, L., & McIntyre, R. S. (2019a). The efficacy of vortioxetine on anhedonia in patients with major depressive disorder. *Frontiers in Psychiatry*, *10*(17), 1-8. https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00017

Cao, B., Zhu, J., Zuckerman, H., Rosenblat, J. D., Brietzke, E., Pan, Z., Subramanieapillai, M., Park, C., Lee, Y., & McIntyre, R. S. (2019b). Pharmacological interventions targeting anhedonia in patients with major depressive disorder: A systematic review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *92*, 109–117. https://doi.org/10.1016/j.pnpbp.2019.01.002

Carpentier, S. M., McCulloch, A. R., Brown, T. M., Faber, S. E. M., Ritter, P., Wang, Z., Salimpoor, V., Shen, K., & McIntosh, A. R. (2020). Complexity matching: brain signals mirror environment information patterns during music listening and reward. *Journal of Cognitive Neuroscience*, *32*(4), 734–745. https://doi.org/10.1162/jocn_a_01508

Ceban, F., Rosenblat, J. D., Kratiuk, K., Lee, Y., Rodrigues, N. B., Gill, H., Subramaniapillai, M., Nasri, F., Lui, L. M. W., Lipsitz, O., Kumar, A., Lee, J. G., Chau, E. H., Cao, B., Lin, K., Ho, R. C., Mansur, R. B., Swainson, J., & McIntyre, R. S. (2021). Prevention and management of common adverse effects of ketamine and esketamine in patients with mood disorders. *CNS Drugs*, *35*(9), 925–934. https://doi.org/10.1007/s40263-021-00846-5

Chanda, M. L., & Levitin, D. J. (2013). The neurochemistry of music. *Trends in Cognitive Sciences*, *17*(4), 179–193. https://doi.org/10.1016/j.tics.2013.02.007

Chmiel, A., & Schubert, E. (2017). Back to the inverted-U for music preference: A review of the literature. *Psychology of Music, 45*(6), 886–909. https://doi.org/10.1177/0305735617697507

Clemente, A., Friberg, A., & Holzapfel, A. (2023). Relations between perceived affect and liking for melodies and visual designs. *Emotion*, *23*(6), 1584–1605. https://doi.org/10.1037/emo0001141

Clepce, M., Gossler, A., Reich, K., Kornhuber, J., & Thuerauf, N. (2010). The relation between depression, anhedonia and olfactory hedonic estimates—A pilot study in

major depression. *Neuroscience Letters*, *471*(3), 139–143. https://doi.org/10.1016/j.neulet.2010.01.027

Colver, M. C., & El-Alayli, A. (2016). Getting aesthetic chills from music: The connection between openness to experience and frisson. *Psychology of Music*, *44*(3), 413–427. https://doi.org/10.1177/0305735615572358

Costa, P. T., & McCrae, R. R. (1992). Normal personality assessment in clinical practice: The NEO Personality Inventory. *Psychological Assessment*, *4*(1), 5–13. https://doi.org/10.1037/1040-3590.4.1.5

Cvrček, P. (2008). Side effects of ketamine in the long-term treatment of neuropathic pain. *Pain Medicine*, *9*(2), 253–257. https://doi.org/10.1111/j.1526-4637.2007.00314.x

Dale, R. M., Bryant, K. A., Finnegan, N., Cromer, K., Thompson, N. R., Altinay, M., & Anand, A. (2020). The NEO-FFI domain of openness to experience moderates ketamine response in treatment resistant depression. *Journal of Affective Disorders*, *260*, 323–328. https://doi.org/10.1016/j.jad.2019.09.010

Daly, E. J., Singh, J. B., Fedgchin, M., Cooper, K., Lim, P., Shelton, R. C., Thase, M. E., Winokur, A., Van Nueten, L., Manji, H., & Drevets, W. C. (2018). Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry*, *75*(2), 139–148. https://doi.org/10.1001/jamapsychiatry.2017.3739

Davis, A. K., Barrett, F. S., & Griffiths, R. R. (2020). Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. *Journal of contextual behavioral science, 15*, 39–45. https://doi.org/10.1016/j.jcbs.2019.11.004

de Fleurian, R., & Pearce, M. T. (2021). Chills in music: A systematic review. *Psychological Bulletin*, *147*(9), 890–920. https://doi.org/10.1037/bul0000341

Der-Avakian, A., & Markou, A. (2012). The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences, 35*(1), 68–77. https://doi.org/10.1016/j.tins.2011.11.005

Deyama, S., & Duman, R. S. (2020). Neurotrophic mechanisms underlying the rapid and sustained antidepressant actions of ketamine. *Pharmacology Biochemistry and Behavior*, *188*, 172837. https://doi.org/10.1016/j.pbb.2019.172837

DeYoung, C. G. (2013). The neuromodulator of exploration: A unifying theory of the role of dopamine in personality. *Frontiers in Human Neuroscience*. *7*, 762. https://doi.org/10.3389/fnhum.2013.00762

DeYoung, C. G., Grazioplene, R. G., & Peterson, J. B. (2012). From madness to genius: The Openness/Intellect trait domain as a paradoxical simplex. *Journal of Research in Personality, 46*(1), 63–78. https://doi.org/10.1016/j.jrp.2011.12.003

Dichter, G. S., Smoski, M. J., Kampov-Polevoy, A. B., Gallop, R., & Garbutt, J. C. (2010). Unipolar depression does not moderate responses to the Sweet Taste Test. *Depression and Anxiety*, *27*(9), 859–863. https://doi.org/10.1002/da.20690

Ding, Y., Ou, Y., Yan, H., Liu, F., Li, H., Li, P., Xie, G., Cui, X., & Guo, W. (2023). Uncovering the neural correlates of anhedonia subtypes in major depressive disorder: Implications for intervention strategies. *Biomedicines*, *11*(12), 1-19. https://doi.org/10.3390/biomedicines11123138

Dittrich, A. (1998). *The standardized psychometric assessment of altered states of consciousness (ASCs) in humans*. PSIN PLUS.

Donnellan, M. B., & Lucas, R. E. (2008). Age differences in the big five across the life span: evidence from two national samples. *Psychology and aging, 23*(3), 558–566. https://doi.org/10.1037/a0012897

Dubé, L., & Le Bel, J. (2003). The content and structure of laypeople's concept of pleasure. *Cognition and Emotion*, *17*(2), 263–295. https://doi.org/10.1080/02699930302295

Ducasse, D., Loas, G., Dassa, D., Gramaglia, C., Zeppegno, P., Guillaume, S., Olié, E., & Courtet, P. (2018). Anhedonia is associated with suicidal ideation independently of depression: A meta-analysis. *Depression and Anxiety*, *35*(5), 382–392. https://doi.org/10.1002/da.22709

Dunn, B. D., German, R. E., Khazanov, G., Xu, C., Hollon, S. D., & DeRubeis, R. J. (2020). Changes in positive and negative affect during pharmacological treatment and cognitive therapy for major depressive disorder: A secondary analysis of two randomized controlled trials. *Clinical Psychological Science*, *8*(1), 36–51. https://doi.org/10.1177/2167702619863427

Dwyer, J. B., Landeros-Weisenberger, A., Johnson, J. A., Londono Tobon, A., Flores, J. M., Nasir, M., Couloures, K., Sanacora, G., & Bloch, M. H. (2021). Efficacy of intravenous ketamine in adolescent treatment-resistant depression: A randomized midazolam-controlled trial. *American Journal of Psychiatry, 178*(4), 352–362. https://doi.org/10.1176/appi.ajp.2020.20010018

Ely, B. A., Nguyen, T. N. B., Tobe, R. H., Walker, A. M., & Gabbay, V. (2021). Multimodal investigations of reward circuitry and anhedonia in adolescent depression. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.678709

Erdem, P., Calum, G., Cowen, P. J., Murphy, S. E., & Harmer, C. J. (2022). A translational perspective on the anti-anhedonic effect of ketamine and its neural underpinnings. *Molecular Psychiatry*, *27*(1), 81–87. https://doi.org/10.1038/s41380-021-01183-1

Fagiolini, A., Florea, I., Loft, H., & Christensen, M. C. (2021). Effectiveness of vortioxetine on emotional blunting in patients with major depressive disorder with inadequate response to SSRI/SNRI treatment. *Journal of Affective Disorders*, *283*, 472–479. https://doi.org/10.1016/j.jad.2020.11.106

Fasano, M. C., Cabral, J., Stevner, A., Vuust, P., Cantou, P., Brattico, E., & Kringelbach, M. L. (2023). The early adolescent brain on music: Analysis of functional dynamics reveals engagement of orbitofrontal cortex reward system. *Human Brain Mapping*, *44*(2), 429–446. https://doi.org/10.1002/hbm.26060

Fayn, K., MacCann, C., Tiliopoulos, N., & Silvia, P. J. (2015). Aesthetic emotions and aesthetic people: Openness predicts sensitivity to novelty in the experiences of interest and pleasure. *Frontiers in Psychology*, *6*, 1877. https://doi.org/10.3389/fpsyg.2015.01877

Fitzgerald, K. C., Morris, B., Soroosh, A., Balshi, A., Maher, D., Kaplin, A., & Nourbakhsh, B. (2021). Pilot randomized active-placebo-controlled trial of low-dose ketamine for the treatment of multiple sclerosis–related fatigue. *Multiple Sclerosis Journal, 27*(6), 942–953. https://doi.org/10.1177/1352458520936226

Franzen, J., & Brinkmann, K. (2016). Anhedonic symptoms of depression are linked to reduced motivation to obtain a reward. *Motivation and Emotion*, *40*(2), 300–308. https://doi.org/10.1007/s11031-015-9529-3

Freitas, C., Manzato, E., Burini, A., Taylor, M. J., Lerch, J. P., & Anagnostou, E. (2018). Neural Correlates of Familiarity in Music Listening: A Systematic Review and a Neuroimaging Meta-Analysis. Frontiers in Neuroscience, 28, 686. https://doi.org/10.3389/fnins.2018.00686

Gabbay, V., Johnson, A. R., Alonso, C. M., Evans, L. K., Babb, J. S., & Klein, R. G. (2015). Anhedonia, but not irritability, is associated with illness severity outcomes in adolescent major depression. *Journal of Child and Adolescent Psychopharmacology*, *25*(3), 194–200. https://doi.org/10.1089/cap.2014.0105

Gaspersz, R., Nawijn, L., Lamers, F., & Penninx, B. W. J. H. (2018). Patients with anxious depression: Overview of prevalence, pathophysiology and impact on course and treatment outcome. *Current Opinion in Psychiatry, 31*(1), 17–25. https://doi.org/10.1097/YCO.0000000000000376

Gastaldon, C., Papola, D., Ostuzzi, G., & Barbui, C. (2019). Esketamine for treatment resistant depression: A trick of smoke and mirrors? *Epidemiology and Psychiatric Sciences*, *29*, 1-4. https://doi.org/10.1017/S2045796019000751

Gebauer, L., Kringelbach, M. L., & Vuust, P. (2012). Ever-changing cycles of musical pleasure: The role of dopamine and anticipation. *Psychomusicology: Music, Mind, and Brain*, *22*(2), 152–167. https://doi.org/10.1037/a0031126.supp

Germans, M. K., & Kring, A. M. (2000). Hedonic deficit in anhedonia: Support for the role of approach motivation. *Personality and Individual Differences*, *28*(4), 659–672. https://doi.org/10.1016/S0191-8869(99)00129-4

Glue, P., Russell, B., & Medlicott, N. J. (2021). Influence of formulation and route of administration on ketamine's safety and tolerability: Systematic review. *European Journal of Clinical Pharmacology*, *77*(5), 671–676. https://doi.org/10.1007/s00228-020-03047-z

Goldberg, L. R. (1990). An alternative „description of personality": The Big-Five factor structure: Journal of Personality and Social Psychology. *Journal of Personality and Social Psychology*, *59*(6), 1216–1229. https://doi.org/10.1037/0022-3514.59.6.1216

Gouveia, R., Cruz, V. T., & Almeida, L. (2022). Sociodemographic and psychological characteristics influencing patients' willingness to participate in clinical trials. BMJ *Open Quality, 11*(4), e002044. https://doi.org/10.1136/bmjoq-2022-002044

Grabski, M., Borissova, A., Marsh, B., Morgan, C. J. A., & Curran, H. V. (2020). Ketamine as a mental health treatment: Are acute psychoactive effects associated with outcomes? A systematic review. *Behavioural Brain Research*, *392*, 112629. https://doi.org/10.1016/j.bbr.2020.112629

Grewe, O., Kopiez, R., & Altenmüller, E. (2009). Chills as an indicator of individual emotional peaks. A*nnals of the New York Academy of Sciences*, *1169*(1), 351–354. https://doi.org/10.1111/j.1749-6632.2009.04783.x

Grewe, O., Nagel, F., Kopiez, R., & Altenmüller, E. (2007). Listening to music as a re-creative process: Physiological, psychological, and psychoacoustical correlates of chills and strong emotions. *Music Perception*, *24*(3), 297–314. https://doi.org/10.1525/mp.2007.24.3.297

Haile, C. N., Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Foulkes, A., Iqbal, S., Mahoney, J. J., III, De La Garza, R., II, Charney, D. S., Newton, T. F., & Mathew, S. J. (2014). Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. *International Journal of*

Neuropsychopharmacology, *17*(2), 331–336. https://doi.org/10.1017/S1461145713001119

Hakulinen, C., Elovainio, M., Pulkki-Råback, L., Virtanen, M., Kivimäki, M., & Jokela, M. (2015). Personality and depressive symptoms: Individual participant meta-analysis of 10 cohort studies. *Depression and Anxiety*, *32*(7), 461–470. https://doi.org/10.1002/da.22376

Halahakoon, D. C., Kieslich, K., O'Driscoll, C., Nair, A., Lewis, G., & Roiser, J. P. (2020). Reward-processing behavior in depressed participants relative to healthy volunteers: A systematic review and meta-analysis. *JAMA Psychiatry*, *77*(12), 1286–1295. https://doi.org/10.1001/jamapsychiatry.2020.2139

Hasselmann, H. (2014). Ketamine as antidepressant? Current state and future perspectives. *Current Neuropharmacology*, *12*(1), 57–70. https://doi.org/10.2174/1570159X113119990043

Hatzigiakoumis, D. S., Martinotti, G., Di Giannantonio, M., & Janiri, L. (2011). Anhedonia and substance dependence: Clinical correlates and treatment options. *Frontiers in Psychiatry*, *2*(10), 1-12. https://www.frontiersin.org/articles/10.3389/fpsyt.2011.00010

Henrich, J., Heine, S. J., & Norenzayan, A. (2010). The weirdest people in the world?. *Behavioral and brain sciences, 33*(2-3), 61-83. https://doi.org/10.1017/S0140525X0999152X

Hillhouse, T. M., & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: From monoamines to glutamate. *Experimental and Clinical Psychopharmacology*, *23*(1), 1–21. https://doi.org/10.1037/a0038550

Ho, N., & Sommers, M. (2013). Anhedonia: A concept analysis. *Archives of Psychiatric Nursing*, *27*(3), 121–129. https://doi.org/10.1016/j.apnu.2013.02.001

Horan, W. P., Kring, A. M., & Blanchard, J. J. (2006). Anhedonia in schizophrenia: A review of assessment strategies. *Schizophrenia Bulletin*, *32*(2), 259–273. https://doi.org/10.1093/schbul/sbj009

Huta, V., & Ryan, R. M. (2010). Pursuing pleasure or virtue: The differential and overlapping well-being benefits of hedonic and eudaimonic motives. *Journal of Happiness Studies*, *11*(6), 735–762. https://doi.org/10.1007/s10902-009-9171-4

Huta, V., & Waterman, A. S. (2014). Eudaimonia and its distinction from hedonia: Developing a classification and terminology for understanding conceptual and

operational definitions. *Journal of Happiness Studies*, *15*(6), 1425–1456. https://doi.org/97-114./10.1007/s10902-013-9485-0

Iadarola, N. D., Niciu, M. J., Richards, E. M., Vande Voort, J. L., Ballard, E. D., Lundin, N. B., Nugent, A. C., Machado-Vieira, R., & Zarate Jr, C. A. (2015). Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. *Therapeutic advances in chronic disease, 6*(3), https://doi.org/10.1177/2040622315579059

Jain, S., Gupta, S., Li, V. W., Suthoff, E., & Arnaud, A. (2022). Humanistic and economic burden associated with depression in the United States: A cross-sectional survey analysis. *BMC Psychiatry*, *22*(1), 2-14. https://doi.org/10.1186/s12888-022-04165-x

Jenkins, L. M., Skerrett, K. A., DelDonno, S. R., Patrón, V. G., Meyers, K. K., Peltier, S., Zubieta, J.-K., Langenecker, S. A., & Starkman, M. N. (2018). Individuals with more severe depression fail to sustain nucleus accumbens activity to preferred music over time. *Psychiatry Research: Neuroimaging*, *275*, 21–27. https://doi.org/10.1016/j.pscychresns.2018.03.002

Jhang, J.-F., Hsu, Y.-H., Jiang, Y.-H., Lee, C.-L., & Kuo, H.-C. (2018). Histopathological characteristics of ketamine-associated uropathy and their clinical association. *Neurourology and Urodynamics*, *37*(5), 1764–1772. https://doi.org/10.1002/nau.23514

Johnston, J. N., Kadriu, B., Allen, J., Gilbert, J. R., Henter, I. D., & Zarate, C. A. (2023). Ketamine and serotonergic psychedelics: An update on the mechanisms and biosignatures underlying rapid-acting antidepressant treatment. *Neuropharmacology*, *226*, 109422. https://doi.org/10.1016/j.neuropharm.2023.109422

Kadriu, B., Greenwald, M., Henter, I. D., Gilbert, J. R., Kraus, C., Park, L. T., & Zarate, C. A., Jr. (2021). Ketamine and serotonergic psychedelics: Common mechanisms underlying the effects of rapid-acting antidepressants. *International Journal of Neuropsychopharmacology*, *24*(1), 8–21. https://doi.org/10.1093/ijnp/pyaa087

Kalsi, S. S., Wood, D. M., & Dargan, P. I. (2011). The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. *Emerging Health Threats Journal*, *4*(1), 7107. https://doi.org/10.3402/ehtj.v4i0.7107

Kashdan, T. B., Biswas-Diener, R., & King, L. A. (2008). Reconsidering happiness: The costs of distinguishing between hedonics and eudaimonia. *The Journal of Positive Psychology*, *3*(4), 219–233. https://doi.org/10.1080/17439760802303044

Khoo, S., & Simms, L. J. (2018). Links between depression and openness and its facets. *Personality and Mental Health*, *12*(3), 203–215. https://doi.org/10.1002/pmh.1417

Kim, J.-W., Suzuki, K., Kavalali, E. T., & Monteggia, L. M. (2023). Bridging rapid and sustained antidepressant effects of ketamine. *Trends in Molecular Medicine*, *29*(5), 364–375. https://doi.org/10.1016/j.molmed.2023.02.003

Klein, D. N., Kotov, R., & Bufferd, S. J. (2011). Personality and depression: Explanatory models and review of the evidence. *Annual review of clinical psychology*, *7*, 269–295. https://doi.org/10.1146/annurev-clinpsy-032210-104540

Klepzig, K., Horn, U., König, J., Holtz, K., Wendt, J., Hamm, A. O., & Lotze, M. (2020). Brain imaging of chill reactions to pleasant and unpleasant sounds. *Behavioural Brain Research*, *380*, 112417. https://doi.org/10.1016/j.bbr.2019.112417

Kopelman, J., Keller, T. A., Panny, B., Griffo, A., Degutis, M., Spotts, C., Cruz, N., Bell, E., Do-Nguyen, K., Wallace, M. L., Mathew, S. J., Howland, R. H., & Price, R. B. (2023). Rapid neuroplasticity changes and response to intravenous ketamine: A randomized controlled trial in treatment-resistant depression. *Translational Psychiatry*, *13*(159). https://doi.org/10.1038/s41398-023-02451-0

Kotov, R., Gamez, W., Schmidt, F., & Watson, D. (2010). Linking "big" personality traits to anxiety, depressive, and substance use disorders: A meta-analysis. *Psychological Bulletin*, *136*(5), 768–821. https://doi.org/10.1037/a0020327

Kringelbach, M. L. (2005). The human orbitofrontal cortex: Linking reward to hedonic experience. *Nature Reviews Neuroscience*, *6*(9), 691–702. https://doi.org/10.1038/nrn1747

Kringelbach, M. L., & Berridge, K. C. (2009). Towards a functional neuroanatomy of pleasure and happiness. *Trends in Cognitive Sciences*, *13*(11), 479–487. https://doi.org/10.1016/j.tics.2009.08.006

Kringelbach, M. L., O'Doherty, J., Rolls, E. T., & Andrews, C. (2003). Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cerebral Cortex*, *13*(10), 1064–1071. https://doi.org/10.1093/cercor/13.10.1064

Krystal, J. H., Sanacora, G., & Duman, R. S. (2013). Rapid-acting glutamatergic antidepressants: The path to ketamine and beyond. *Biological Psychiatry*, *73*(12), 1133–1141. https://doi.org/10.1016/j.biopsych.2013.03.026

Kudo, Y., Nakagawa, A., Wake, T., Ishikawa, N., Kurata, C., Nakahara, M., Nojima, T., & Mimura, M. (2017). Temperament, personality, and treatment outcome in major

depression: A 6-month preliminary prospective study. *Neuropsychiatric Disease and Treatment*, *13*, 17–24. https://doi.org/10.2147/NDT.S123788

Lally, N., Nugent, A. C., Luckenbaugh, D. A., Niciu, M. J., Roiser, J. P., & Zarate, C. A. (2015). Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. *Journal of Psychopharmacology*, *29*(5), 596–607. https://doi.org/10.1177/0269881114568041

Laursen, D. R., Nejstgaard, C. H., Bjørkedal, E., Frost, A. D., Hansen, M. R., Paludan-Müller, A. S., Prosenz, J., Werner, C. P., & Hróbjartsson, A. (2023). Impact of active placebo controls on estimated drug effects in randomised trials: A systematic review of trials with both active placebo and standard placebo. *The Cochrane Database of Systematic Reviews, 3*(3). https://doi.org/10.1002/14651858.MR000055.pub2

Layer, R. T., Popik, P., Olds, T., & Skolnick, P. (1995). Antidepressant-like actions of the polyamine site NMDA antagonist, eliprodil (SL-82.0715). *Pharmacology Biochemistry and Behavior, 52*(3), 621–627. https://doi.org/10.1016/0091-3057(95)00155-P

Le, T. T., Cordero, I. P., Jawad, M. Y., Swainson, J., Di Vincenzo, J. D., Jaberi, S., Phan, L., Lui, L. M. W., Ho, R., Rosenblat, J. D., & McIntyre, R. S. (2022). The abuse liability of ketamine: A scoping review of preclinical and clinical studies. *Journal of Psychiatric Research*, *151*, 476–496. https://doi.org/10.1016/j.jpsychires.2022.04.035

Leder, H., Belke, B., Oeberst, A., & Augustin, D. (2004). A model of aesthetic appreciation and aesthetic judgments. *British Journal of Psychology*, *95*, 489–508. https://doi.org/10.1348/0007126042369811

Lépine, J.-P., & Briley, M. (2011). The increasing burden of depression. *Neuropsychiatric Disease and Treatment*, *7*(1), 3–7. https://doi.org/10.2147/NDT.S19617

Li, N., Lee, B., Liu, R.-J., Banasr, M., Dwyer, J. M., Iwata, M., Li, X.-Y., Aghajanian, G., & Duman, R. S. (2010). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*, *329*(5994), 959–964. https://doi.org/10.1126/science.1190287

Li, Y., Dong, Z., Wen, G., Ren, X., Ren, W., Yan, L., Wang, X., Yu, H., Wu, X., Xia, X., Lu, Y., & Wu, X. (2021). Long-term ketamine administration induces bladder damage and upregulates autophagy-associated proteins in bladder smooth muscle tissue. *Environmental Toxicology*, *36*(12), 2521–2529. https://doi.org/10.1002/tox.23365

Liang, S., Y, W., Hanxiaoran, L., Greenshaw, A. J., & T, L. (2022). Anhedonia in depression and schizophrenia: Brain reward and aversion circuits. *Neuropsychiatric Disease and Treatment*, *18*, 1385–1396. https://doi.org/10.2147/NDT.S367839

Lii, T. R., Smith, A. E., Flohr, J. R., Okada, R. L., Nyongesa, C. A., Cianfichi, L. J., Hack, L. M., Schatzberg, A. F., & Heifets, B. D. (2023). Randomized trial of ketamine masked by surgical anesthesia in patients with depression. *Nature Mental Health, 1*(11), 876–886. https://doi.org/10.1038/s44220-023-00140-x

Liu, X., Li, L., Li, M., Ren, Z., & Ma, P. (2021). Characterizing the subtype of anhedonia in major depressive disorder: A symptom-specific multimodal MRI study. *Psychiatry Research: Neuroimaging*, *308*, 1-9. https://doi.org/10.1016/j.pscychresns.2020.111239

Llorca, P., & Gourion, D. (2015). Management of anhedonia and depressive symptoms in depressed outpatients: Benefit for functioning. *European Psychiatry*, *30*(1). https://doi.org/10.1016/S0924-9338(15)31881-2

Loas, G. (1996). Vulnerability to depression: A model centered on anhedonia. *Journal of Affective Disorders*, *41*(1), 39–53. https://doi.org/10.1016/0165-0327(96)00065-1

Luckenbaugh, D. A., Niciu, M. J., Ionescu, D. F., Nolan, N. M., Richards, E. M., Brutsche, N. E., Guevara, S., & Zarate, C. A. (2014). Do the dissociative side effects of ketamine mediate its antidepressant effects? *Journal of Affective Disorders*, *159*, 56–61. https://doi.org/10.1016/j.jad.2014.02.017

Lundin, N. B., Niciu, M. J., Luckenbaugh, D. A., Ionescu, D. F., Richards, E. M., Voort, J. L. V., Brutsche, N. E., Machado-Vieira, R., & C. A. Zarate, J. (2014). Baseline Vitamin B12 and Folate Levels Do Not Predict Improvement in Depression After a Single Infusion of Ketamine. *Pharmacopsychiatry*, *47*(0), 141-144. https://doi.org/10.1055/s-0034-1377042

Mahler, S. V., Smith, K. S., & Berridge, K. C. (2007). Endocannabinoid hedonic hotspot for sensory pleasure: Anandamide in nucleus accumbens shell enhances „liking“ of a sweet reward. *Neuropsychopharmacology*, *32*(11), 2267–2278. https://doi.org/10.1038/sj.npp.1301376

Mas-Herrero, E., Maini, L., Sescousse, G., & Zatorre, R. J. (2021). Common and distinct neural correlates of music and food-induced pleasure: A coordinate-based meta-analysis of neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *123*, 61–71. https://doi.org/10.1016/j.neubiorev.2020.12.008

Matveychuk, D., Thomas, R. K., Swainson, J., Khullar, A., MacKay, M.-A., Baker, G. B., & Dursun, S. M. (2020). Ketamine as an antidepressant: Overview of its mechanisms of action and potential predictive biomarkers. *Therapeutic Advances in Psychopharmacology*, *10*, 1-21. https://doi.org/10.1177/2045125320916657

Maurizio, F., Freeman, M. P., Flynn, M., Judge, H., Hoeppner, B. B., Cristina, C., Ionescu, D. F., Mathew, S. J., Chang, L. C., Iosifescu, D. V., Murrough, J., Debattista, C., Schatzberg, A. F., Trivedi, M. H., Jha, M. K., Gerard, S., Wilkinson, S. T., & Papakostas, G. I. (2020). Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Molecular Psychiatry*, *25*(7), 1592–1603. https://doi.org/10.1038/s41380-018-0256-5

Mazza, M., Squillacioti, M. R., Pecora, R. D., Janiri, L., & Bria, P. (2009). Effect of aripiprazole on self-reported anhedonia in bipolar depressed patients. *Psychiatry Research*, *165*(1), 193–196. https://doi.org/10.1016/j.psychres.2008.05.003

McCrae, R. R. (2007). Aesthetic chills as a universal marker of openness to experience. *Motivation and Emotion*, *31*(1), 5–11. https://doi.org/10.1007/s11031-007-9053-1

McCrae, R. R., & Costa, P. T. (1983). Joint factors in self-reports and ratings: Neuroticism, extraversion and openness to experience. *Personality and Individual Differences*, *4*(3), 245–255. https://doi.org/10.1016/0191-8869(83)90146-0

McCrae, R. R., & Costa, P. T. (1987). Validation of the five-factor model of personality across instruments and observers. *Journal of Personality and Social Psychology*, *52*(1), 81–90. https://doi.org/10.1037/0022-3514.52.1.81

McCrae, R. R., & Costa, P. T. (1989). The structure of interpersonal traits: Wiggins's circumplex and the five-factor model. *Journal of Personality and Social Psychology*, *56*(4), 586–595. https://doi.org/10.1037/0022-3514.56.4.586

McFarland, B. R., & Klein, D. N. (2009). Emotional reactivity in depression: diminished responsiveness to anticipated reward but not to anticipated punishment or to nonreward or avoidance. *Depression and anxiety, 26*(2), 117-122. https://doi.org/10.1002/da.20513

McIntyre, R. S., Rosenblat, J. D., Nemeroff, C. B., Sanacora, G., Murrough, J. W., Berk, M., Brietzke, E., Dodd, S., Gorwood, P., Ho, R., Iosifescu, D. V., Lopez Jaramillo, C., Kasper, S., Kratiuk, K., Lee, J. G., Lee, Y., Lui, L. M. W., Mansur, R. B., Papakostas, G. I., … Stahl, S. (2021). Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available

evidence and implementation. *American Journal of Psychiatry*, *178*(5), 383–399. https://doi.org/10.1176/appi.ajp.2020.20081251

McMakin, D. L., Olino, T. M., Porta, G., Dietz, L. J., Emslie, G., Clarke, G., Wagner, K. D., Asarnow, J. R., Ryan, N. D., Birmaher, B., Shamseddeen, W., Mayes, T., Kennard, B., Spirito, A., Keller, M., Lynch, F. L., Dickerson, J. F., & Brent, D. A. (2012). Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment–resistant depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(4), 404–411. https://doi.org/10.1016/j.jaac.2012.01.011

Meshkat, S., Ho, R. C., Cao, B., Teopiz, K. M., Rosenblat, J. D., Rhee, T. G., Di Vincenzo, J. D., Ceban, F., Jawad, M. Y., & McIntyre, R. S. (2023). Biomarkers of ketamine's antidepressant effect: An umbrella review. *Journal of Affective Disorders*, *323*, 598–606. https://doi.org/10.1016/j.jad.2022.12.021

Microsoft Corporation. (2018). Microsoft Excel. https://office.microsoft.com/excel

Mion, G., & Villevieille, T. (2013). Ketamine pharmacology: An update (pharmacodynamics and molecular aspects, recent findings). *CNS Neuroscience & Therapeutics*, *19*(6), 370–380. https://doi.org/10.1111/cns.12099

Mkrtchian, A., Evans, J. W., Kraus, C., Yuan, P., Kadriu, B., Nugent, A. C., Roiser, J. P., & Zarate, C. A. (2021). Ketamine modulates fronto-striatal circuitry in depressed and healthy individuals. *Molecular Psychiatry*, *26*(7), 3292–3301. https://doi.org/10.1038/s41380-020-00878-1

Modlin, N. L., Miller, T. M., Rucker, J. J., Kirlic, N., Lennard-Jones, M., Schlosser, D., & Aaronson, S. T. (2023). Optimizing outcomes in psilocybin therapy: Considerations in participant evaluation and preparation. *Journal of Affective Disorders*, *326*, 18–25. https://doi.org/10.1016/j.jad.2023.01.077

Montejo, A. L., Prieto, N., de Alarcón, R., Casado-Espada, N., de la Iglesia, J., & Montejo, L. (2019). Management strategies for antidepressant-related sexual dysfunction: A clinical approach. *Journal of Clinical Medicine*, *8*(10), 1-19. https://doi.org/10.3390/jcm8101640

Mulder, R. T. (2002). Personality pathology and treatment outcome in major depression: A review. *American Journal of Psychiatry*, *159*(3), 359–371. https://doi.org/10.1176/appi.ajp.159.3.359

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., Iqbal, S., Pillemer, S., Foulkes, A., Shah, A., Charney, D. S., & Mathew, S. J. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: A Two-

Site Randomized Controlled Trial. *American Journal of Psychiatry*, *170*(10), 1134–1142. https://doi.org/10.1176/appi.ajp.2013.13030392

Muscat, S.-A., Hartelius, G., Crouch, C. R., & Morin, K. W. (2021). An integrative approach to ketamine therapy may enhance multiple dimensions of efficacy: Improving therapeutic outcomes with treatment resistant depression. *Frontiers in Psychiatry*, *12*, 710338. https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.710338

Muthukumaraswamy, S. D., Forsyth, A., & Lumley, T. (2021). Blinding and expectancy confounds in psychedelic randomized controlled trials. *Expert Review of Clinical Pharmacology, 14*(9), 1133–1152. https://doi.org/10.1080/17512433.2021.1933434

Naito, M., Kato, M., Koshikawa, Y., Bandou, H., Sakai, S., Takekita, Y., Nishida, K., & Kinoshita, T. (2022). Personality as a basis for antidepressant selection for patients with depression: A two-point outcome study at 4 and 8 weeks. *Journal of Affective Disorders*, *314*, 27–33. https://doi.org/10.1016/j.jad.2022.07.001

Nemati, S., Akrami, H., Salehi, S., Esteky, H., & Moghimi, S. (2019). Lost in music: Neural signature of pleasure and its role in modulating attentional resources. *Brain Research*, *1711*, 7–15. https://doi.org/10.1016/j.brainres.2019.01.011

Newton-Howes, G., Tyrer, P., Johnson, T., Mulder, R., Kool, S., Dekker, J., & Schoevers, R. (2014). Influence of personality on the outcome of treatment in depression: Systematic review and meta-analysis. *Journal of Personality Disorders*, *28*(4), 577–593. https://doi.org/10.1521/pedi_2013_27_070

Niciu, M. J., Henter, I. D., Luckenbaugh, D. A., Zarate, C. A., & Charney, D. S. (2014). Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: Ketamine and other compounds. *Annual Review of Pharmacology and Toxicology, 54*(1), 119–139. https://doi.org/10.1146/annurev-pharmtox-011613-135950

Nikayin, S., Murphy, E., Krystal, J. H., & Wilkinson, S. T. (2022). Long-term safety of ketamine and esketamine in treatment of depression. *Expert Opinion on Drug Safety*, *21*(6), 777–787. https://doi.org/10.1080/14740338.2022.2066651

Nikolin, S., Rodgers, A., Schwaab, A., Bahji, A., Zarate, C., Vazquez, G., & Loo, C. (2023). Ketamine for the treatment of major depression: A systematic review and meta-analysis. *eClinicalMedicine*, *62*, 102127. https://doi.org/10.1016/j.eclinm.2023.102127

Nogo, D., Jasrai, A. K., Kim, H., Nasri, F., Ceban, F., Lui, L. M. W., Rosenblat, J. D., Vinberg, M., Ho, R., & McIntyre, R. S. (2022). The effect of ketamine on anhedonia: Improvements in dimensions of anticipatory, consummatory, and motivation-related reward deficits. *Psychopharmacology*, *239*(7), 2011–2039. https://doi.org/10.1007/s00213-022-06105-9

Nostro, A. D., Müller, V. I., Varikuti, D. P., Pläschke, R. N., Hoffstaedter, F., Langner, R., Patil, K. R., & Eickhoff, S. B. (2018). Predicting personality from network-based resting-state functional connectivity. *Brain Structure and Function*, *223*(6), 2699–2719. https://doi.org/10.1007/s00429-018-1651-z

Nowak, G., Li, Y., & Paul, I. A. (1996). Adaptation of cortical but not hippocampal NMDA receptors after chronic citalopram treatment. *European Journal of Pharmacology, 295*(1), 75–85. https://doi.org/10.1016/0014-2999(95)00585-4

Nugent, A. C., Ballard, E. D., Gould, T. D., Park, L. T., Moaddel, R., Brutsche, N. E., & Zarate, C. A. (2019). Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects. *Molecular Psychiatry, 24*(7), 1040–1052. https://doi.org/10.1038/s41380-018-0028-2

Nusbaum, E. C., & Silvia, P. J. (2011). Shivers and timbres: Personality and the experience of chills from music. *Social Psychological and Personality Science*, *2*(2), 199–204. https://doi.org/10.1177/1948550610386810

Nutt, D., Demyttenaere, K., Janka, Z., Aarre, T., Bourin, M., Canonico, P. L., Carrasco, J. L., & Stahl, S. (2007). The other face of depression reduced positive affect: The role of catecholamines in causation and cure. *Journal of Psychopharmacology*, *21*(5), 461–471. https://doi.org/10.1177/0269881106069938

Passie, T., Adams, H.-A., Logemann, F., Brandt, S. D., Wiese, B., & Karst, M. (2021). Comparative effects of (*S*)-ketamine and racemic (*R/S*)-ketamine on psychopathology, state of consciousness and neurocognitive performance in healthy volunteers. *European Neuropsychopharmacology*, *44*, 92–104. https://doi.org/10.1016/j.euroneuro.2021.01.005

Paul, R., Schaaff, N., Padberg, F., Möller, H.-J., & Frodl, T. (2009). Comparison of racemic ketamine and S-ketamine in treatment-resistant major depression: Report of two cases. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *10*(3), 241–244. https://doi.org/10.1080/15622970701714370

Peciña, S., Smith, K. S., & Berridge, K. C. (2006). Hedonic hot spots in the brain. *The Neuroscientist*, *12*(6), 500–511. https://doi.org/10.1177/1073858406293154

Perkovic, S. J. M., & Pechenkov, I. G. (2023). Personality predictors of anhedonia and depression: The role of the big five, autonomy, and sociotropy. *Personality and Individual Differences, 208*, 112158. https://doi.org/10.1016/j.paid.2023.112158

Permoda-Osip, A., Dorszewska, J., Bartkowska-Sniatkowska, A., Chlopocka-Wozniak, M., & Rybakowski, J. K. (2013). Vitamin B12 Level may be related to the efficacy of single ketamine infusion in bipolar depression. *Pharmacopsychiatry*, *46*(6), 227–228. https://doi.org/10.1055/s-0033-1349861

Phillips, J. L., Norris, S., Talbot, J., Birmingham, M., Hatchard, T., Ortiz, A., Owoeye, O., Batten, L. A., & Blier, P. (2019). Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: A randomized controlled trial. *American Journal of Psychiatry*, *176*(5), 401–409. https://doi.org/10.1176/appi.ajp.2018.18070834

Price, R. B., & Duman, R. (2020). Neuroplasticity in cognitive and psychological mechanisms of depression: An integrative model. *Molecular Psychiatry*, *25*(3), 530–543. https://doi.org/10.1038/s41380-019-0615-x

Rad, M. S., Martingano, A. J., & Ginges, J. (2018). Toward a psychology of Homo sapiens: Making psychological science more representative of the human population. *Proceedings of the National Academy of Sciences of the United States of America, 115*(45), 11401–11405. https://www.jstor.org/stable/10.2307/26563156

Rademacher, L., Kraft, D., Eckart, C., & Fiebach, C. J. (2023). Individual differences in resilience to stress are associated with affective flexibility. *Psychological Research, 87*(6), 1862–1879. https://doi.org/10.1007/s00426-022-01779-4

Ran, L.-Y., Liu, X.-Y., Wang, W., Tao, W.-Q., Xiang, J.-J., Zeng, Q., Kong, Y.-T., Zhang, C.-Y., Liao, J., Qiu, H.-T., & Kuang, L. (2024). Personality traits predict treatment outcome of an antidepressant in untreated adolescents with depression: An 8-week, open-label, flexible-dose study. *Journal of Affective Disorders*, *350*, 102–109. https://doi.org/10.1016/j.jad.2024.01.015

R Core Team. (2021). R: A language and environment for statistical computing. *R Foundation for Statistical Computing*. https://www.R-project.org/

Reybrouck, M., & Eerola, T. (2022). Musical enjoyment and reward: From hedonic pleasure to eudaimonic listening. *Behavioral Sciences*, *12*(5), 154. https://doi.org/10.3390/bs12050154

Ribot, T. (1896). La Psychologie des Sentiment [The Psychology of Feelings]. Paris: Alcan.

Rizvi, S. J., Pizzagalli, D. A., Sproule, B. A., & Kennedy, S. H. (2016). Assessing anhedonia in depression: Potentials and pitfalls. *Neuroscience & Biobehavioral Reviews*, *65*, 21–35. https://doi.org/10.1016/j.neubiorev.2016.03.004

Rodrigues, N. B., McIntyre, R. S., Lipsitz, O., Cha, D. S., Lee, Y., Gill, H., Majeed, A., Phan, L., Nasri, F., Ho, R., Lin, K., Subramaniapillai, M., Kratiuk, K., Mansur, R. B., & Rosenblat, J. D. (2020). Changes in symptoms of anhedonia in adults with major depressive or bipolar disorder receiving IV ketamine: Results from the Canadian Rapid Treatment Center of Excellence. *Journal of Affective Disorders*, *276*, 570–575. https://doi.org/10.1016/j.jad.2020.07.083

Rømer Thomsen, K. (2015). Measuring anhedonia: Impaired ability to pursue, experience, and learn about reward. *Frontiers in Psychology*, *6,* 1-11. https://www.frontiersin.org/journals/psychology/articles/10.3389/fpsyg.2015.01409

Rømer Thomsen, K., Whybrow, P. C., & Kringelbach, M. L. (2015). Reconceptualizing anhedonia: Novel perspectives on balancing the pleasure networks in the human brain. *Frontiers in Behavioral Neuroscienc,* 9(49), 1-23. https://doi.org/10.3389/fnbeh.2015.00049

Rong, C., Park, C., Rosenblat, J. D., Subramaniapillai, M., Zuckerman, H., Fus, D., Lee, Y. L., Pan, Z., Brietzke, E., Mansur, R. B., Cha, D. S., Lui, L. M. W., & McIntyre, R. S. (2018). Predictors of response to ketamine in treatment resistant major depressive disorder and bipolar disorder. *International Journal of Environmental Research and Public Health*, *15*(4), 1-10. https://doi.org/10.3390/ijerph15040771

Ross, S. R., Lutz, C. J., & Bailley, S. E. (2002). Positive and negative symptoms of schizotypy and the five-factor model: A domain and facet level analysis. *Journal of Personality Assessment, 79*(1), 53–72. https://doi.org/10.1207/S15327752JPA7901_04 https://doi.org/10.1073/pnas.1721165115

RStudio Team. (2020). RStudio: Integrated Development for R. *RStudio, PBC.* http://www.rstudio.com/

Sakurai, H., Hoeppner, B., Jain, F., Foster, S., Pedrelli, P., Mischoulon, D., Fava, M., & Cusin, C. (2022). Use of Staging Models for Treatment-Resistant Depression Is Not Helpful in Predicting Nonresponse to Acute Intravenous Ketamine Treatment. *Journal of Clinical Psychopharmacology*, *42*(2), 140-145. https://doi.org/10.1097/JCP.0000000000001524

Saland, S. K., Schoepfer, K. J., & Kabbaj, M. (2016). Hedonic sensitivity to low-dose ketamine is modulated by gonadal hormones in a sex-dependent manner. *Scientific Reports*, *6*(1), 1-16. https://doi.org/10.1038/srep21322

Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., & Zatorre, R. J. (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nature Neuroscience*, *14*(2), 257–262. https://doi.org/10.1038/nn.2726

Salimpoor, V. N., Benovoy, M., Longo, G., Cooperstock, J. R., & Zatorre, R. J. (2009). The rewarding aspects of music listening are related to degree of emotional arousal. *PLOS ONE*, *4*(10), e7487. https://doi.org/10.1371/journal.pone.0007487

Sanacora, G., Frye, M. A., McDonald, W., Mathew, S. J., Turner, M. S., Schatzberg, A. F., Summergrad, P., Nemeroff, C. B. (2017). A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*, *74*(4), 399-405. https://doi.org/10.1001/jamapsychiatry.2017.0080

Sassano-Higgins, S., Baron, D., Juarez, G., Esmaili, N., & Gold, M. (2016). A review of ketamine abuse and diversion. *Depression and Anxiety*, *33*(8), 718–727. https://doi.org/10.1002/da.22536

Serretti, A. (2023). Anhedonia and depressive disorders. *Clinical Psychopharmacology and Neuroscience: The Official Scientific Journal of the Korean College of Neuropsychopharmacology*, *21*(3), 401–409. https://doi.org/10.9758/cpn.23.1086

Shao, X., & Zhu, G. (2020). Associations among monoamine neurotransmitter pathways, personality traits, and major depressive disorder. *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.00381

Sherdell, L., Waugh, C. E., & Gotlib, I. H. (2012). Anticipatory pleasure predicts motivation for reward in major depression. *Journal of Abnormal Psychology*, *121*(1), 51–60. https://doi.org/10.1037/a0024945

Shiroma, P. R., Thuras, P., Wels, J., Sophia, A. C., Erbes, C., Susannah, T., & Lim, K. O. (2020). A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. *Translational Psychiatry, 10*(1). https://doi.org/10.1038/s41398-020-00897-0

Short, B., Fong, J., Galvez, V., Shelker, W., & Loo, C. K. (2018). Side-effects associated with ketamine use in depression: A systematic review. *The Lancet Psychiatry*, *5*(1), 65–78. https://doi.org/10.1016/S2215-0366(17)30272-9

Sial, O. K., Parise, E. M., Parise, L. F., Gnecco, T., & Bolaños-Guzmán, C. A. (2020). Ketamine: The final frontier or another depressing end? *Behavioural Brain Research*, *383*, 112508. https://doi.org/10.1016/j.bbr.2020.112508

Silvia, P. J. (2005). Emotional responses to art: From collation and arousal to cognition and emotion. *Review of General Psychology*, *9*(4), 342–357. https://doi.org/10.1037/1089-2680.9.4.342

Silvia, P. J., Fayn, K., Nusbaum, E. C., & Beaty, R. E. (2015). Openness to experience and awe in response to nature and music: Personality and profound aesthetic experiences. *Psychology of Aesthetics, Creativity, and the Arts*, *9*(4), 376–384. https://doi.org/10.1037/aca0000028

Singh, J. B., Fedgchin, M., Daly, E. J., De Boer, P., Cooper, K., Lim, P., Pinter, C., Murrough, J. W., Sanacora, G., Shelton, R. C., Kurian, B., Winokur, A., Fava, M., Manji, H., Drevets, W. C., & Van Nueten, L. (2016). A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *American Journal of Psychiatry*, *173*(8), 816–826. https://doi.org/10.1176/appi.ajp.2016.16010037

Singh, B., Vande Voort, J. L., Riva-Posse, P., Pazdernik, V. M., Frye, M. A., & Tye, S. J. (2023). Ketamine-associated change in anhedonia and mTOR expression in treatment-resistant depression. *Biological Psychiatry*, *93*(12), e65–e68. https://doi.org/10.1016/j.biopsych.2022.10.007

Słupski, J., Cubała, W. J., Górska, N., Słupska, A., & Gałuszko-Węgielnik, M. (2020). Copper and anti-anhedonic effect of ketamine in treatment-resistant depression. *Medical Hypotheses*, *144*, 110268. https://doi.org/10.1016/j.mehy.2020.110268

Small, D. M., Zatorre, R. J., Dagher, A., Evans, A. C., & Jones-Gotman, M. (2001). Changes in brain activity related to eating chocolate: From pleasure to aversion. *Brain*, *124*(9), 1720–1733. https://doi.org/10.1093/brain/124.9.1720

Smigielski, L., Kometer, M., Scheidegger, M., Krähenmann, R., Huber, T., & Vollenweider, F. X. (2019). Characterization and prediction of acute and sustained response to psychedelic psilocybin in a mindfulness group retreat. *Scientific Reports, 9*(1), 14914. https://doi.org/10.1038/s41598-019-50612-3

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. *The British Journal of Psychiatry*, *167*(1), 99–103. https://doi.org/10.1192/bjp.167.1.99

Sofia, R. D., & Harakal, J. J. (1975). Evaluation of ketamine HCl for anti-depressant activity. *Archives Internationales de Pharmacodynamie et de Therapie*, *214*(1), 68–74.

Soto, C. J., & John, O. P. (2017). The next Big Five Inventory (BFI-2): Developing and assessing a hierarchical model with 15 facets to enhance bandwidth, fidelity, and predictive power. *Journal of Personality and Social Psychology, 113*(1), 117–143. https://doi.org/10.1037/pspp0000096

Storr, T. M., & Quibell, R. (2009). Can ketamine prescribed for pain cause damage to the urinary tract? *Palliative Medicine*, *23*(7), 670–672. https://doi.org/10.1177/0269216309106828

Studerus, E., Gamma, A., & Vollenweider, F. X. (2010). Psychometric Evaluation of the Altered States of Consciousness Rating Scale (OAV). *PLoS One*, *5*(8), e12412. https://doi.org/10.1371/journal.pone.0012412

Sumpf, M., Jentschke, S., & Koelsch, S. (2015). Effects of aesthetic chills on a cardiac signature of emotionality. *PLoS One*, *10*(6), e0130117. https://doi.org/10.1371/journal.pone.0130117

Swiecicki, L., Zatorski, P., Bzinkowska, D., Sienkiewicz-Jarosz, H., Szyndler, J., & Scinska, A. (2009). Gustatory and olfactory function in patients with unipolar and bipolar depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *33*(5), 827–834. https://doi.org/10.1016/j.pnpbp.2009.03.030

Szpunar, K. K., Schellenberg, E. G., & Pliner, P. (2004). Liking and Memory for Musical Stimuli as a Function of Exposure. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 30*(2), 370–381. https://doi.org/10.1037/0278-7393.30.2.370

Takahashi, M., Shirayama, Y., Muneoka, K., Suzuki, M., Sato, K., & Hashimoto, K. (2013). Low openness on the revised NEO Personality Inventory as a risk factor for treatment-resistant depression. *PLoS One*, *8*(9), e71964. https://doi.org/10.1371/journal.pone.0071964

ten Have, M., de Graaf, R., van Dorsselaer, S., Tuithof, M., Kleinjan, M., & Penninx, B. W. J. H. (2018). Recurrence and chronicity of major depressive disorder and their risk indicators in a population cohort. *Acta Psychiatrica Scandinavica*, *137*(6), 503–515. https://doi.org/10.1111/acps.12874

Tiihonen, M., Brattico, E., Maksimainen, J., Wikgren, J., & Saarikallio, S. (2017). Constituents of music and visual-art related pleasure – a critical integrative literature review. *Frontiers in Psychology*, *8*, 1218. https://doi.org/10.3389/fpsyg.2017.01218

Tobe, R. H., Tu, L., Keefe, J. R., Breland, M. M., Ely, B. A., Sital, M., Richard, J. T., Tural, U., Iosifescu, D. V., & Gabbay, V. (2023). Personality characteristics, not clinical symptoms, are associated with anhedonia in a community sample: A preliminary investigation. *Journal of Psychiatric Research*, *168*, 221–229. https://doi.org/10.1016/j.jpsychires.2023.10.044

Treadway, M. T., & Zald, D. H. (2011). Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neuroscience & Biobehavioral Reviews*, *35*(3), 537–555. https://doi.org/10.1016/j.neubiorev.2010.06.006

Trøstheim, M., Eikemo, M., Meir, R., Hansen, I., Paul, E., Kroll, S. L., Garland, E. L., & Leknes, S. (2020). Assessment of anhedonia in adults with and without mental illness: A systematic review and meta-analysis. *JAMA network open*, *3*(8), e2013233. https://doi.org/10.1001/jamanetworkopen.2020.13233

Vesna, L., Yang, Y., Ivana, F., & Per, S. (2021). Ketamine decreases neuronally released glutamate via retrograde stimulation of presynaptic adenosine A1 receptors. *Molecular Psychiatry*, *26*(12), 7425–7435. https://doi.org/10.1038/s41380-021-01246-3

Verhaeghen, P. (2018). Once More, with Feeling: The role of familiarity in the aesthetic response. *The Psychological Record, 68*(3), 379–384. https://doi.org/10.1007/s40732-018-0312-1

Vinckier, F., Gourion, D., & Mouchabac, S. (2017). Anhedonia predicts poor psychosocial functioning: Results from a large cohort of patients treated for major depressive disorder by general practitioners. *European Psychiatry*, *44*, 1–8. https://doi.org/10.1016/j.eurpsy.2017.02.485

Vollenweider, F. X., & Kometer, M. (2010). The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. *Nature Reviews Neuroscience*, *11*(9), 642–651. https://doi.org/10.1038/nrn2884

Vrieze, E., Demyttenaere, K., Bruffaerts, R., Hermans, D., Pizzagalli, D. A., Sienaert, P., Hompes, T., de Boer, P., Schmidt, M., & Claes, S. (2014). Dimensions in major depressive disorder and their relevance for treatment outcome. *Journal of Affective Disorders*, *155*, 35–41. https://doi.org/10.1016/j.jad.2013.10.020

Vrieze, E., Pizzagalli, D. A., Demyttenaere, K., Hompes, T., Sienaert, P., de Boer, P., Schmidt, M., & Claes, S. (2013). Reduced reward learning predicts outcome in major depressive disorder. *Biological Psychiatry*, *73*(7), 639–645. https://doi.org/10.1016/j.biopsych.2012.10.014

Wang, Y.-B., Song, N.-N., Ding, Y.-Q., & Zhang, L. (2023). Neural plasticity and depression treatment. *IBRO Neuroscience Reports*, *14*, 160–184. https://doi.org/10.1016/j.ibneur.2022.09.001

Wardenaar, K. J., Conradi, H. J., Bos, E. H., & Jonge, P. de. (2014). Personality modulates the efficacy of treatment in patients with major depressive disorder. *The Journal of Clinical Psychiatry*, *75*(9), 14188. https://doi.org/10.4088/JCP.13m08855

Warraich, Z., & Kleim, J. A. (2010). Neural plasticity: The biological substrate for neurorehabilitation. *PM&R*, *2*(12), 208–219. https://doi.org/10.1016/j.pmrj.2010.10.016

Watanabe, K., Fujimoto, S., Marumoto, T., Kitagawa, T., Ishida, K., Nakajima, T., Moriguchi, Y., Fujikawa, K., & Inoue, T. (2022). Therapeutic potential of vortioxetine for anhedonia-like symptoms in depression: A post hoc analysis of data from a clinical trial conducted in Japan. *Neuropsychiatric Disease and Treatment*, *18*, 363–373. https://doi.org/10.2147/NDT.S340281

World Health Organization. (2021). Depression. https://www.who.int/newsroom/fact-sheets/detail/depression

World Health Organization. (2022). COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide. https://www.who.int/news/item/02-03-2022- covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide

Widnyana, M. G., Senapathi, T. G. A., Aryani, L. N. A., & Ryalino, C. (2023). The role of ketamine as an antidepressant agent. *Bali Journal of Anesthesiology*, *7*(2), 57-59. https://doi.org/10.4103/bjoa.bjoa_81_23

Wilkinson, S. T., Cristan, F., Ballard, E. D., Mathew, S. J., Grunebaum, M. F., Murrough, J. W., Sos, P., Wang, G., Ralitza, G., & Zarate, C. A. (2019). Impact of midazolam vs. saline on effect size estimates in controlled trials of ketamine as a rapid-acting antidepressant. *Neuropsychopharmacology, 44*(7), 1233–1238. https://doi.org/10.1038/s41386-019-0317-8

Winer, E. S., Nadorff, M. R., Ellis, T. E., Allen, J. G., Herrera, S., & Salem, T. (2014). Anhedonia predicts suicidal ideation in a large psychiatric inpatient sample. *Psychiatry Research*, *218*(1), 124–128. https://doi.org/10.1016/j.psychres.2014.04.016

Yates, C., Kruse, J. L., Price, J. B., Robertson, A. A. B., & Tye, S. J. (2021). Modulating neuroplasticity: lessons learned from antidepressants and emerging novel

therapeutics. *Current Treatment Options in Psychiatry*, *8*(4), 229–257. https://doi.org/10.1007/s40501-021-00249-9

Yavi, M., Lee, H., Henter, I. D., Park, L. T., & Zarate, C. A. (2022). Ketamine treatment for depression: A review. *Discover Mental Health*, *2*(1). https://doi.org/10.1007/s44192-022-00012-3

Zajonc, R. B. (1968). Attitudinal effects of mere exposure. *Journal of Personality and Social Psychology, 9*(2), 1-27. https://doi.org/10.1037/h0025848

Zarate, C. A., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., Charney, D. S., & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *ARCH GEN PSYCHIATRY*, *63*(8), 856-864. https://doi.org/10.1001/archpsyc.63.8.856

Zatorre, R. J. (2015). Musical pleasure and reward: Mechanisms and dysfunction. *Annals of the New York Academy of Sciences*, *1337*(1), 202–211. https://doi.org/10.1111/nyas.12677

Zeki, S. (2013). Clive Bell's "Significant Form" and the neurobiology of aesthetics. *Frontiers in Human Neuroscience, 7*, 730.https://doi.org/10.3389/fnhum.2013.00730

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List of Abbreviations

5D-ASC	5-Dimensional Altered States of Consciousness
AES	Aesthetic Experiences Scale
AIC	Akaike information criteria
AMPA	Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BNDF	Brain-Derived Neurotrophic Factor
BIC	Bayesian Information Criterion
BMRQ	Barcelona Music Reward Questionnaire
DARS	Dimensional Anhedonia Rating Scale
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
NEO-FFI	NEO Five-Factor Inventory
NMDA	N-Methyl-D-Aspartate
TEPS	Temporal Experience of Pleasure Scale
TRD	Treatment-Resistant Depression
VAS	Visual Analogue Scale

Appendix

Abstract

Background: Ketamine has shown promise as a treatment for anhedonia by restoring and enhancing hedonic experiences. However, the use of ketamine is associated with side effects and concerns about long-term risks. Therefore, the appropriateness of ketamine treatment needs to be carefully considered and predictors of its efficacy should be identified. The personality trait of openness appears to be a predictor of anhedonia and to have a positive effect on the subjective experience of ketamine and on the efficacy of ketamine in treating depression. Openness may therefore be a valuable predictor of the hedonic effects of ketamine. ***Method:*** Data from a larger project (N=46, M_{age}=24.46) with healthy participants receiving both ketamine and placebo were used to examine the influence of openness (NEO-FFI) on hedonic experiences (elicited by music). Furthermore, the interaction between openness and treatment condition and the influence of openness on experienced anxiety during ketamine infusion (5D-ASC) were analyzed. ***Results:*** Openness had no effect on hedonic responses, and no interaction was found between openness and the treatment condition in influencing hedonic responses. Openness did not influence anxiety, nor did anxiety mediate the relationship between openness and hedonic response. ***Discussion:*** Results suggest that openness has no effect on the hedonic response following ketamine administration. As the original project was not designed to address this question, the results should be interpreted with caution. Further studies are needed to understand the influence of the personality trait openness on the pro-hedonic effects of ketamine and to advance the field of personalized medicine.

Abstract (German Version)

Hintergrund: Ketamin hat sich als erfolgversprechende Behandlungsmethode für Anhedonie erwiesen, indem es hedonische Erfahrungen steigert. Die Anwendung von Ketamin ist jedoch mit Nebenwirkungen und Bedenken hinsichtlich Langzeitfolgen verbunden. Daher sollte die Angemessenheit einer Ketamin Behandlung sorgfältig geprüft und Prädiktoren für ihre Wirksamkeit identifiziert werden. Das Persönlichkeitsmerkmal Offenheit scheint ein Prädiktor für Anhedonie zu sein und einen positiven Einfluss auf das subjektive Erleben von Ketamin und die Wirksamkeit von Ketamin bei der Behandlung von Depressionen zu haben. Offenheit könnte daher ein wertvoller Prädiktor für die hedonische Wirkung von Ketamin sein. ***Methode***: Daten eines größeren Forschungsprojektes (N=46, M_{alter}=24.46) mit gesunden Teilnehmer*innen, die sowohl Ketamin als auch Placebo erhielten, wurden verwendet, um den Einfluss von Offenheit (NEO-FFI) auf hedonische Erfahrungen (induziert durch Musik) zu untersuchen. Zudem wurde die Interaktion zwischen Offenheit und Behandlungsbedingung sowie der Einfluss von Offenheit auf die erlebte Angst während der Ketamin-Infusion (5D-ASC) analysiert. ***Ergebnisse:*** Offenheit hatte keinen Einfluss auf die hedonischen Reaktionen und es wurde keine Interaktion zwischen Offenheit und Behandlungsbedingung bezüglich der hedonischen Reaktionen gefunden. Offenheit beeinflusste weder die erlebte Angst während der Ketamin-Infusion noch vermittelte Angst die Beziehung zwischen Offenheit und hedonischer Reaktion. ***Diskussion:*** Die Ergebnisse deuten darauf hin, dass Offenheit keinen Einfluss auf die hedonische Reaktion nach der Verabreichung von Ketamin hat. Da das ursprüngliche Projekt nicht für diese Fragestellung konzipiert war, sollten die Ergebnisse mit Vorsicht interpretiert werden. Weitere Studien sind notwendig, um den Einfluss der Persönlichkeitseigenschaft Offenheit auf die pro-hedonistische Wirkung von Ketamin zu verstehen und den Bereich der personalisierten Medizin voranzubringen.

Supplemental Tables

Table A1

Sample Sizes and Descriptive Statistics for Each Hypothesis

Characteristics	Categories	Baseline Dataset		Treatment Dataset	
		N	*M (SD)*	*N*	*M (SD)*
N		42	-	38	-
Gender	Men	17	-	17	-
	Women	25	-	21	-
Age		-	24.04 (3.70)	-	23.52 (3.25)

Note. Baseline dataset was used for Hypothesis 1. Treatment dataset was used for Hypotheses 2 and 3.

Tabel A2

Variable Distribution across Datasets

Characteristics	Categories	Baseline Dataset	Treatment Dataset
		M (SD)	*M (SD)*
Openness		35.81 (4.92)	36.79 (4.29)
Hedonic Response	Baseline	7.69 (1.30)	-
	Placebo	-	7.32 (1.25)
	Ketamine	-	7.42 (1.34)
Anxiety	Placebo	-	2.24 (8.12)
	Ketamine	-	80.53 (109.24)

Note. Baseline dataset was used for Hypothesis 1. Treatment dataset was used for Hypotheses 2 and 3.