EEG Markers of Ketamine-Induced Ego Dissolution:

A Predictive Coding perspective of the Psychedelic Bayesian brain

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Thesis submitted for the degree of
Master in Cognitive Neuroscience
60 credits

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UNIVERSITY OF OSLO

Spring 2023

"Add quote"

– André Nilsen, 2023

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Abstract

Psychedelic research and clinical applications are currently booming. Among these new treatment options, ketamine has demonstrated rapid symptom alleviation in depression, substance use disorder, and chronic pain. Although the importance of set and setting in treatment outcome has received much focus, the importance of the experience itself is still poorly understood. This study aims to investigate potential EEG markers of ego dissolution during ketamine infusion in a repeated measures design. We recruited seven healthy participants to quantify that received sub-anesthetic ketamine doses. Based on previous studies, potential EEG markers of ego dissolution include power spectral density and Lempel-Ziv complexity. To measure ego dissolution, participants were periodically awoken during their session and instructed to report if they were experiencing ego dissolution. The ego dissolution scores were then used to group and compare EEG data. We found no significant group differences in power bands or signal diversity between ego dissolution and non-ego dissolution. However, we did find significant group-wise differences between the baseline eyes closed measure and ketamine in the alpha power band and Lempel-Ziv complexity supporting previous findings. Taken together, these results indicate that ego dissolution might not be different from other psychedelic brain states if the null hypothesis is true. The results were also not in accordance with the predictive coding framework, which posits that ego dissolution brain states generate more change in prior beliefs than compared to other psychedelic states, our results, however, did not support this interpretation. However, the study had serious limitations and future work should strive to reproduce our study with higher power or investigate other potential markers of ego dissolution.

Contents

1 INTRODUCTION

1.1 Psychedelic therapy for mental disorders

Unipolar depression currently affects around 5% of the adult population, with an estimated 10% of t) life time prevalence of depression globally (Lim et al., 2018). The societal burden of depression in the US was around $236 billion in 2018 (American Psychiatric Association, 2021), with the average cost of treatment per patient per year around $5000 (Gauthier et al., 2017). Psychotherapy and medication tend to have small effect sizes (Munder et al., 2019) and often alleviate depressive symptoms more than the quality of life (Kamenov et al., 2017). In response to the current inefficient treatment paradigms, the use of psychedelic compounds like ketamine, psilocybin, and MDMA is being explored (Cavarra et al., 2022). Given the revival of psychedelic research popularity, it is important to study when and how these compounds work and how to utilize them to the greatest effect. In this thesis, we focus on the role of specific psychedelic experiences in therapeutic outcomes in general and, specifically, if these can be detected.

The emerging 'age of psychiatry' (Barber & Aaronson, 2022), marked by an expanding array of psychedelic treatment options, has shown promising results in combating disorders such as PTSD, anxiety, depression, and substance abuse (Tupper et al., 2015). Compared to standard treatment options, psychedelic therapy has larger immediate effects (Luoma et al., 2020), short-term treatment plans (Penn et al., 2021; Cherry, 2021), and lower relapse rates (Vargas et al., 2020). Psychedelic therapy has since been employed to treat Post-Traumatic Stress Disorder, depression, anxiety, and substance use disorder (Nutt et al., 2020). With the renewed interest in psychedelic research and clinical use, a range of important questions has arisen: What is the importance of set and setting in psychedelic therapy? Can we detect changes in neural dynamics? How can we better guide treatment practices? What are the underlying physiological and psychological mechanisms that underpin alteration in symptomatology?

Here we will focus primarily on ketamine as ketamine is one of the

most accessible and rapidly adopted psychedelic substances currently available to treat unipolar depression. Ketamine has been used since the 1960s as an anesthetic in hospitals worldwide (Li & Vlisides, 2016). Its accessibility, safety profile, and established use make it an ideal candidate for optimizing therapeutic frameworks, leading to its application in treating major depression, chronic pain, and substance dependency (Li & Vlisides, 2016). Nevertheless, ketamine therapy is not globally accepted as a legal treatment option for depression (Tafra, 2023). Further, the National Health Service in the UK warns that about 10% of patients may experience adverse effects when using ketamine, and some may even experience worsened symptoms (Oxford Health NHS Foundation Trust, 2022). Additionally, the efficacy of ketamine treatment varies greatly among patients, and the reason for this variability is unclear. A review of ketamine therapy against depression surveyed over the last decades of progress suggests that the evidence is limited by bias, small sample sizes, and a lack of data on confounding factors (Li & Vlisides, 2016).

The varied response rate to ketamine therapy and longevity suggest that it is worth studying which factors influence these responses and potentially test ways in which these can be manipulated. While numerous studies have focused on the pharmacological and physiological effects of psychedelics (see box 1), comparatively little has been done on the cognitive and phenomenological (i.e., subjective experience) effects that might affect treatment outcomes (Vlisides et al., 2018). Research on other psychedelic compounds, like psilocybin, provide some empirical evidence for the role of psychedelic experiences in treatment efficacy. For instance, in a double-blind psilocybin study (Griffiths et al., 2008), 36 hallucinogenic naïve adults received either psilocybin or methylphenidate - a placebo - and reported their subjective experiences during treatment. 14 months later, the researchers observed significant correlations between the participants' subjective experience and well-being. These results exemplify potential psychological mechanisms that have been overseen so far in the psychedelic literature.

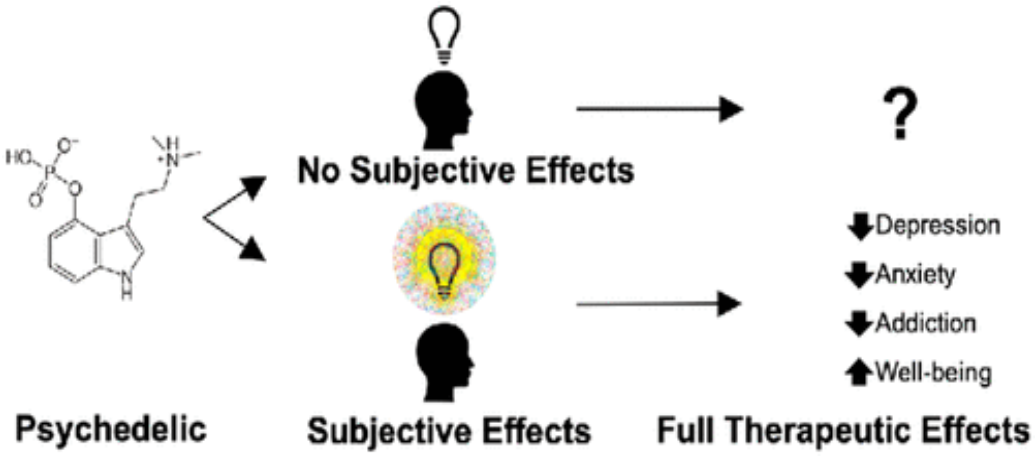

Illustration 1: *This overview was borrowed from Yaden & Griffiths (2021). It illustrates the assumed importance of subjective experience to achieve more efficient treatment. Although the literature is more complicated than shown above, it provides a limited framework for approaching psychedelic therapy.*

Box 1: Pharmacological and physiological studies of ketamine

Pharmacological studies on the biological mechanisms of ketamine have asserted the influence of ketamine on glutamatergic pyramidal neurons by manipulating NMDA antagonists. In early studies during the 80s, researchers found decreased inhibition of GABAergic neurons through NMDA antagonist activation (Anis et al., 1983), which projected onto post-synaptic glutamatergic cortical pyramidal neurons and increased their excitation (Thomson et al., 1985). Studies on knockout mice with altered GluRε1 gene expression - expressing an NMDAR subunit - demonstrated less responsiveness to ketamine than control mice (Petrenko et al., 2004). Later, it was postulated that GABAergic inhibition of glutamatergic interneurons mediates disinhibition and psychosis by diminishing the inhibitory control of prefrontal cortex neurons (Homayoun & Mohaddam, 2007).

Most physiological studies have considered the potential side effects of ketamine. Studies have demonstrated that ketamine may induce vestibular-type symptoms like dizziness, nausea, and vomiting (Li & Vlisides, 2016). In addition, increased heart rate and intracranial

pressure, although the latter has rarely been observed. Ketamine is generally considered safe, although it has mild to medium addiction potential, and frequent ketamine consumption increases cystitis symptoms probability three to four-fold (Anderson et al., 2022)

1.2 The role of subjective experience in psychedelic therapy

Classic psychedelics tend to induce visual hallucinations, altered perception of time and space, a mixing of senses (synesthesia), and mystical experiences - characterized as encounters with the divine and altered sense of self (Barrett & Griffiths, 2018). These changes in consciousness are highly sensitive to the subject's set (i.e., mindset or state of mind) and setting (environment and context) before, during, and after, the experience (Carhart-Harris et al., 2018). One well-known mystical experience that can occur during consumption of psychedelics is ego dissolution. Ego dissolution is the loss of self and experience of unity with the external[1] and is considered a potential mechanism in treatment efficacy because patients suffering from depression or anxiety might be experiencing ego resistance, in which alterations to their self-beliefs are resistant to change (Stoliker et al., 2022). For example, a self-belief about their academic short-commings might change or their perceived lack of social skills. Therefore, ego dissolution might enable patients to consider their own beliefs more flexibly, in a new light of themself in relation to the external world brought on by the temporary loss of selfhood. In the following section, we explore ego dissolution and mystical experiences in depth from the perspective of psychedelic therapy in general, and ketamine in particular.

[1]The word "external" is difficult to use in this setting because many experience that there is no boundary between self and "other" during ego dissolution. They may for instance experience everything as internal or in the same dimension. Language often creates these barriers.

1.2.1 Mystical experiences and ego dissolution

Mystical experiences and ego dissolution are two interconnected phenomena often observed in the context of psychedelic therapy. Scientifically, mystical experiences refer to profound, transcendent encounters characterized by a sense of unity, sacredness, and ineffability (Barrett & Griffiths, 2018). These experiences have been associated with positive therapeutic outcomes in treating various psychological disorders (Barber & Aaronson, 2022). On the other hand, ego dissolution refers to the temporary disintegration of one's sense of self or identity, leading to a feeling of merging with a larger whole (Nour et al., 2016). Both phenomena share certain qualities, such as altered perception, a sense of interconnectedness, and the potential for long-lasting personal transformation. However, they can be differentiated by the focus on the dissolution of self-boundaries in ego dissolution, whereas mystical experiences encompass a broader range of spiritual and ineffable elements which might also include ego dissolution (Nour et al., 2016). Despite their differences, both mystical experiences and ego dissolution might contribute significantly to the therapeutic potential of psychedelic substances (Roseman et al., 2018).

1.2.2 Subjective experiences in psychedelic therapy

Research on mystical experiences within psychedelic therapy has attracted growing interest. Ko et al. (2022) conducted a meta-analysis that identified a direct correlation between treatment outcomes and mystical experiences, utilizing psilocybin, ayahuasca, and ketamine to address depression, cancer-related distress, and substance abuse. Furthermore, the authors maintain that improved predictors of mystical experience intensity are essential for optimizing positive results. In another insightful meta-study, Hirschfield et al. (2021) analyzed 17 psilocybin therapy studies from the last decades. They found a positive correlation between the ketamine infusion total dosage and both perceptual alterations and positively experienced ego dissolution or *Oceanic Boundlessness* - i.e., derealization, depersonalization and positive mood. They also observed minimal effect of dosage on negative mood, underscoring the importance of dose in

therapeutic efficacy, possibly mediated by the effect of ego dissolution.

While several systematic reviews have shown that psychedelic therapy correlates positively with well-being and mystical experiences, such as ego dissolution and connectedness (Roseman et al., 2018), these reviews have also revealed nuances. A recent meta-analysis on psilocybin and 5-MeO-DMT partially supported the importance of ego dissolution in treatment outcome (Wellander & Marchese, 2022). Three of the five studies found a moderate negative correlation between ego dissolution and symptom prevalence in depression and anxiety. The other two studies showed weak to no correlation. Likewise, Kałużna et al. (2022) conducted a mixed review of 15 studies on classical psychedelics, each with varying designs. All the studies measured well-being and mystical experiences, including ego dissolution and connectedness. Their analysis revealed that both ego dissolution and connectedness were associated with symptom improvement following psychedelic therapy in four of the seven studies included. Notably, the researchers found that ego dissolution led to immediate psychological improvement, while connectedness was associated with more sustained positive emotions (Kałużna et al., 2022). Although meta-studies can provide a general outlook on the potential psychological mechanisms, it often lacks the in-depth clues as to why the treatment is efficient.

Individual studies can also provide further insights into the significance of the psychedelic experience in treatment effectiveness. For example, in a recent psilocybin study by Roseman et al., (2018) investigated the role of mystical experience in treating treatment-resistant depression (TR-D). The study utilized the Altered States of Consciousness questionnaire to measure two constructs: Oceanic Boundlessness (OBN) and Dread of Ego Dissolution (DED). OBN is similar to positive ego dissolution as a state of bliss and unity, while DED is more related to anxiety and discomfort (Roseman et al., 2018). The results revealed a significant difference between low and high OBN groups and Quick Inventory Depression Scale Self Report (QIDS-SR) at all times up to five weeks following the psilocybin session. Interestingly, the study found that DED and OBN explained 54% of the observed variance in QIDS-SR

scores. These results indicate that positively experienced ego dissolution - i.e., oceanic boundlessness - might be an important ingredient to successful treatment. Similarly, avoiding unpleasant experiences might also contribute to improved symptom alleviation.

1.2.3 Subjective experiences in ketamine therapy

Although the above mentioned results are promising, the picture is not so clear for the role of mystical experiences and ego dissolution in the particular case of ketamine therapy. Ketamine therapy has recently become a popular intervention for vulnerable clinical groups, such as treatment-resistant depression (TR-D) patients and substance-abuse users (Walsh et al., 2021). The rest of the thesis will focus on ketamine therapy and attempt to understand its importance in treatment outcomes better and whether it can be measured clinically.

As ketamine therapy efficacy continues to be explored, it is crucial to consider the role of various phenomenological aspects, such as mystical experiences and ego dissolution, in enhancing therapeutic outcomes. Both mystical experiences and ego dissolution are important aspects of ketamine therapy. Understanding the interplay between these phenomena and their impact on individual responses to therapy may help unravel the reasons for the observed variability in ketamine's efficacy. It might also suggest ways to optimize therapeutic frameworks involving psychedelic substances.

Box 2: Biological and psychological effects of ketamine

As described in Box 1, ketamine is a dissociative anesthetic consisting of S-and R enantiomers (Matthew & Zarate, 2016, p. 13). Most researchers advocate the disinhibition hypothesis (see Illustration 2), which states that ketamine binds to the NMDA receptor antagonistically on GABAergic projections to downstream glutamatergic pyramidal neurons (Alshammari, 2020). This, in turn, disinhibits the glutamatergic neurons, leading to increased glutamatergic activity,

neuroplasticity, and connectivity in the prefrontal cortex (Moghaddam et al., 1997).

Ketamine's rapid antidepressant effects are believed to stem from several changes in brain activity. For instance, ketamine tends to activate signal pathways like the mammalian target of rapamycin (mTOR) and increased brain-derived neurotrophic factors (BDNF) (Matthew & Zarate, 2016). Both of the latter signal cascades have been shown to induce neuroplastic changes in their target area. Other potential mediators of ketamine's antidepressant effect include NMDAR-mediated burst suppression of the lateral habenula. This brain region processes reward-related stimuli and negative signals in the reward circuitry (Alshammari, 2020). Rodent studies have demonstrated correlations between burst suppression in this region, synchronized theta activity, and depressive symptoms. Taken together, these biological mechanisms are non-linear complex interactions that nurture many interpretations and possible markers.

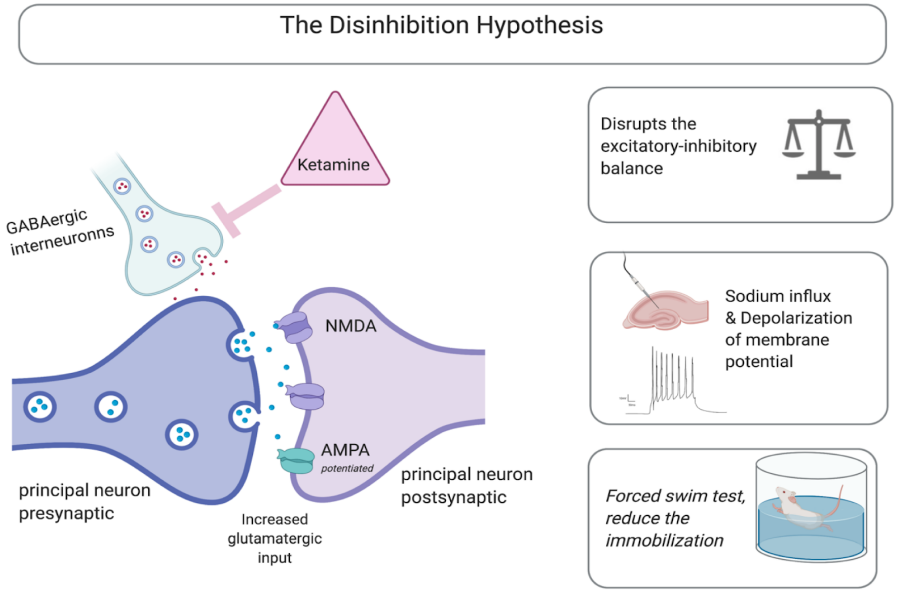

Illustration 2: *This illustration was borrowed from Alshammari (2020). It depicts the disinhibition hypothesis in biological terms.*

Research on the role of phenomenology in ketamine therapy primarily

focuses on the relationship between dissociation, a common psychedelic effect of ketamine use (Mathew & Zarate, 2016), and antidepressant response. However, it is important to note that dissociation and ego dissolution are distinct experiences (Sleight et al., 2023). Dissociation is similar to the annihilation component of ego dissolution, comprising derealisation, depersonalization, and amnesia. Furthermore, as mentioned earlier, it lacks the relational connectedness component found in ego dissolution, which is often assumed to mediate long-term therapeutic improvement (Kałużna et al., 2022). In other words, dissociation is similar to ego dissolution but lacks the - arguably most important - relational aspect.

Although dissociation and ego dissolution are distinct concepts, studying the role of dissociation in ketamine treatment efficacy can provide some insight into the expected effects of ego dissolution. For instance, Niciu et al. (2018) conducted a meta-study examining the impact of dissociation on the antidepressant effects of ketamine therapy. The study revealed a significant correlation between depersonalization - detachment from oneself - and the Hamilton Depression Rating Scale (HAM-D). However, derealization - detachment from one's surroundings - influenced the HAM-D in only one out of three studies (Niciu et al., 2018). Moreover, the total score on the Clinician-Administered Dissociative State Scale (CADSS), which includes derealization, depersonalization, and amnesia, did not correlate with HAM-D. However, Luckenbaugh et al. (2014) found a moderate correlation between the global CADSS score and HAM-D change. Overall, these findings suggest that detachment from oneself might be the most critical aspect of ketamine therapy to achieve good results. However, the degree of dissociation does not explain all the variance in treatment efficacy.

A clear example of the unexplained treatment variation was demonstrated in a 2016 literature review by Ballard & Zarate (2016). They summarized the relationship between dissociation and the antidepressant effects in treatment-resistant depression (TR-D) patients undergoing ketamine therapy as being mixed. Only three of the eight studies reviewed found a correlation between CADSS and the antidepressant response. The amount of variance explained in these studies ranged from 12 to 21 percent

(Ballard & Zarate, 2016). Interestingly, they also observed that other measures, such as blood pressure and psychotic or manic symptoms, appeared unable to predict treatment response.

Recent evidence has shed light on the confusion surrounding the role of dissociation in ketamine therapy. For example, a phase 3 clinical trial conducted by Chen et al. (2022) investigated the relationship between dissociation and the antidepressant effects of ketamine in patients with treatment-resistant depression. Surprisingly, the study found no significant correlation between dissociation and antidepressant effect. However, it is important to note that this trial utilized esketamine, a nasal spray that has been shown to exhibit fewer dissociative effects compared to racemic ketamine, which contains both S and R enantiomers (Ballard & Zarate, 2020). These results could suggest that reaching a certain dissociative threshold is necessary to achieve additional impact on treatment efficacy. Moreover, studies comparing the efficacy of racemic ketamine and esketamine have revealed that despite racemic ketamine being more potent and dissociative, it demonstrated higher remission rates, higher overall response rates, and lower dropout rates (Bahji et al., 2021). Meanwhile, other researchers claim that there is no relationship between the degree of dissociation and antidepressant effects (McIntyre et al., 2021) while citing evidence that contradicts their claim. These findings underscore the need for more research to clarify the role of the psychedelic experience in ketamine therapy.

Most existing research on ketamine has prioritized exploring the role of dissociation in treatment response efficacy. However, the potential benefits of ego dissolution - a less extensively studied but potentially more promising aspect of ketamine therapy (Roseman et al., 2018) - have yet to be fully investigated.

1.3 Measuring ego dissolution

1.3.1 Questionnaires

To measure ego dissolution accurately, various questionnaires have been utilized, such as the Altered States of Consciousness (ASC) questionnaire, the Mystical Experiences Questionnaire (MEQ), and the Ego Dissolution Inventory (EDI) (Nour et al., 2016). These questionnaires all measure ego dissolution as a compromised sense of self and a dissolved boundary between the subject and object representation, commonly referred to as ego death, ego loss, ego disintegration, or self-loss (Nour et al., 2016; Sleight et al., 2023). The MEQ captures this experience as the *unitive experience* factor, while the ASC measures it as the *Oceanic Boundlessnes*s item. However, the EDI is the only questionnaire that explicitly measures ego dissolution.

1.3.2 Neural markers

Questionnaires like EDI, or post-treatment interviews, might be good tools to measure subjectively experienced ego dissolution, dissociation, and other phenomena characteristic of psychoactive compounds like ketamine. However, such methods can only be performed post-treatment. Therefore, a tool based on neural activity that can detect such experiences live is valuable. Such a tool could then be employed in the clinic to better calibrate titration levels, duration, and other parameters, to maximize the effectiveness of treatment.

The predictive coding theory is a well-known theory of brain processes that provides a framework to interpret changes in brain activity. The theory was based on the free energy principle developed by Karl Friston in 2010 (Friston, 2010). The main assumption is that the brain is a prediction machine designed to minimize the degree of surprise or “prediction error" (Friston et al., 2012). By minimizing the degree of uncertainty, the organism can maximize the utility of the environment and achieve optimal functioning (den Ouden et al., 2012). Although the model has received some criticism - like the “black box problem" - it has generally reached a

consensus (Millidge et al., 2022).

From the predictive coding perspective, hierarchical structures like the cerebral cortex consist of higher layers manipulating baseline activity in lower levels based on predicted activity patterns and the lower levels returning the prediction error (Alamia & VanRullen, 2019). Alpha power has been suggested to mediate the predicted signals from higher to lower network levels, and Alamia & VanRullen (2019) claim that predictive coding might be impossible without alpha power. Their results found alpha oscillations elicited forward waves during sensory processing and backward waves when incoming sensory stimuli were absent (Alamia & VanRullen, 2019). This fits the idea of alpha power as a top-down control marker synchronizing activity across the brain during sensory processing. By extension, decreased alpha power leads to more entropic brain activity and higher prediction errors (Bazanova & Vernon, 2014). The relationship between alpha power and predictive coding has implications for understanding the neural mechanisms underlying altered states of consciousness, such as those induced by ketamine therapy. In this context, recent studies have explored the potential use of alpha power as a neural marker of ego dissolution during ketamine therapy.

Several studies have attempted to identify potential neural markers of ego dissolution in ketamine therapy. One such study by Vlisides and colleagues (2018) investigated the neural correlates of altered states of consciousness using electroencephalography (EEG) in patients who received a subanesthetic dose of 0.5 mg/kg ketamine over 40 minutes. The study found that the administration of ketamine decreased alpha power in the parietal and occipital channels. This decrease in alpha power was thought to indicate increased uncertainty in the system, as alpha power is associated with synchrony across brain regions. Interestingly, these alpha power changes were correlated with experiences of ego transcendence, which involves a temporary loss of sense of self while remaining aware of the surroundings and experiencing disembodiment. Since ego transcendence is similar to the subcomponents of ego dissolution, these findings suggest that alpha power could be a valuable potential marker of ego dissolution. However, it is worth noting that the dose used in

this study was relatively low, which may limit the likelihood of patients experiencing ego dissolution in standard ketamine therapy.

Farnes and colleagues (2020) conducted a study to investigate the effects of subanesthetic doses of ketamine on signal diversity and altered states of consciousness. They measured EEG signal diversity in 17 healthy volunteers who received up to 1 mg/kg/h of ketamine and found that it was strongly correlated with the experience of unity and anxiety in the eyes-open condition and complex imagery and elementary imagery in the eyes-closed condition. These findings fit that of Schartner et al. (2017), who demonstrated a positive correlation between signal complexity and overall mystical experience and a discriminatory strong correlation between signal complexity and ego dissolution in 19 healthy male volunteers. These studies suggest signal complexity may be a useful predictor of ego dissolution during ketamine therapy. This is consistent with the predictive coding idea that synchrony and top-down control decrease during ketamine-induced ego dissolution. However, it is worth noting that the study by Schartner et al. (2017) excluded females from participation, which may limit the generalizability of the findings.

Other studies have emphasized the correlation between ego dissolution and functional connectivity. Tagliazucchi et al. (2016) measured fMRI in 15 participants receiving LSD or a placebo. They found strong correlates between functional connectivity density and ego dissolution score (Tagliazucchi et al., 2016). Other studies demonstrate large-scale network alterations in connectivity during psychedelic sessions. For instance, studies have found decreased functional connectivity in the default mode network (DMN) - often associated with self-referential thought and inward attention - for LSD and psilocybin (Carhart-Harris et al., 2012, Müller et al., 2018). Stoliker et al. (2022) argue that a decrease in the DMN is likely associated with ego dissolution and might reflect the dissolution of prior beliefs regarding the self. In addition, DMN is often assumed to control top-down inhibition of sensory signals. Moreover, functional connectivity between the DMN and Salience Network (SN) tends to increase during psychedelic-induced ego dissolution (Carhart-Harris et al., 2013). Taken together, decreased DMN intra-connectivity

and increased DMN-SN inter-connectivity might mediate less top-down control and increase the bottom-up influences, which can help generate or update beliefs (Stoliker et al., 2022).

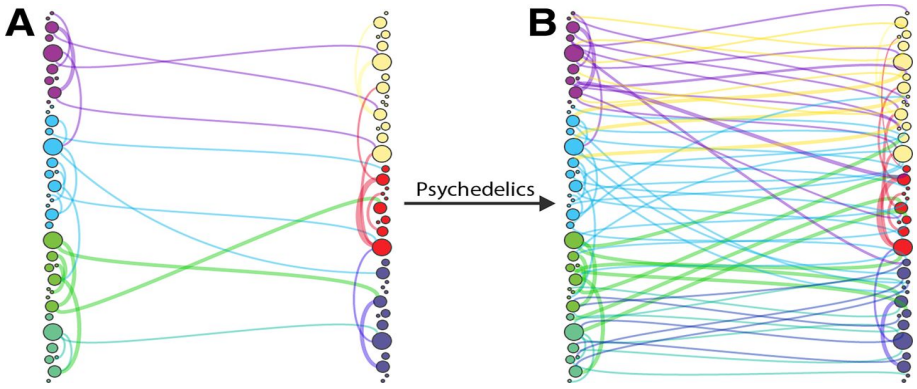

Illustration 3: *This is an illustrative comparison between a sober and psychedelic state in brain complexity. The illustration was borrowed from Stoliker et al. (2022). The main advantage of classical psychedelics and, by extension, ketamine is that they provide the formation of new neural pathways and rewire old patterns. This is only possible by decreasing the top-down predictive modulation of information and allowing new interpretations according to the predictive coding theory.*

In addition to research on markers of ego dissolution, a recent study also provided some clues to potential markers of dissociation. Salle et al. (2016) administered ketamine to 21 healthy participants and measured their brain activity with EEG. Their results indicated that depersonalization correlated with alpha power reductions in general and frontal regions like the prefrontal cortex and anterior cingulate cortex (Salle et al., 2016). Independent of the degree of depersonalization, they also found increased gamma power and decreased slow wave (alpha, beta, delta) frequencies.

Overall, alpha power in occipital and parietal regions, perhaps frontal as well, Lempel-Ziv complexity and Amplitude Coalition Entropy might provide effective markers of ego dissolution in EEG activity. Furthermore, both functional connectivity within DMN and between DMN and SN could provide useful markers as well for both EEG and fMRI data.

1.4 The current study

This study aims to investigate EEG markers of ego dissolution in healthy volunteers in order to inform future studies aimed at the clinical. To achieve this, we will administer sub-anesthetic ketamine doses to healthy participants and measure their degree of ego dissolution during the intervention by using an intermittent awakening paradigm (IAP). In an IAP the subject is "awakened" or “aroused" by external stimulation (saying their name out loud and squeezing the trapezius muscle). This allows us to get subjective reports of experience (such as ego dissolution) closer to the time period when the experience happened. Thus, during an awakening (when the subject responds reliably to external stimuli), we aim to ask them whether they experienced ego dissolution by use of a shortened questionnaire (see appendix 8.2). Based on their response, we can then label the time period preceding the awakening as either ego dissolution (ED) or non-ego dissolution (NED). We will then compare ED and NED periods of EEG-based frequency band power in the five canonical EEG bands and signal diversity.

Based on previous findings, we expect decreased alpha power in parietal, frontal, and occipital areas and increased signal complexity for the ego dissolution condition compared to non-ego dissolution.

2 METHODS

This study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (REK), application number: 2015/1520. All participants gave written consent to participate in the study.

2.1 Participants

Seven participants were recruited using convenience sampling. Participants were excluded if they were younger than 18 or older than 35. Additionally, we also excluded participants with neurological diseases and those that were unable to lay still for an extended period of time. The recruited participants were all male (M: 26.5, SD: 2.9, R: [23 - 32]). While ketamine is considered a safe pharmacological agent in widespread clinical use (Matthew & Zarate, 2016, p. 59), we employed screening methods (see 2.2.1) to minimize potential negative effects caused by contra-indications such as pre-existing conditions, stress, anxiety, or other factors that might be negative predictors. This was in accordance with established guidelines for research on psychoactive compounds (Vollenweider & Preller, 2020). No participants were excluded during screening or in the analysis phase. None of the participants received any form of payment or compensation for participation to not incentivize participation beyond intrinsic motivation.

2.2 Procedure

Experiments were conducted at Kongsberg Hospital with the presence of a licensed anesthesiologist who administered the ketamine (see 2.2.2) and ensured the safety of the participant.

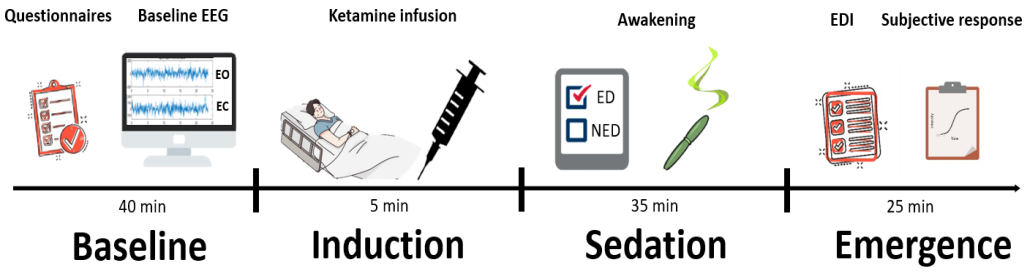

Illustration 3: *Graphical overview of the study. Baseline included demographic questionnaire and mood, and baseline EEG measures like eyes closed (EC) and eyes open (EO). Induction consisted of participants receiving intravenous ketamine infusion. Sedation consisted of periodical awakenings with inquiries of ego dissolution and working memory tasks. Emergence only contained a few psychedelic questionnaires, questions of their experience and participants drawing subjective response curves.*

2.2.1 Prescreening

On the day of the session, participants were first assessed using the Mini International Neuropsychiatric Interview to establish fitness to join the study (Sheehan et al., 1998). We checked specifically for contraindications like schizophrenia, substance abuse, and mood disorders. Finally, a holistic evaluation was performed based on general communication with the participant, including whether they seemed relaxed, understood the received information about the study, and consented to participate free of secondary motivation such as a history of substance abuse. Given that these criteria were satisfactory, the participant would be accepted to the study and driven to Kongsberg Hospital with the research team.

2.2.2 Psychometric assessment

Prior to the intervention, the participants answered a series of questionnaires: A short demographic questionnaire designed to map age, gender, and general habits; the Montgomery and Åsberg Depression Rating Scale (MADSR) to measure depressive symptoms (Montgomery & Ås-

berg, 1979); the State-Trait Anxiety Inventory (STAI-5) to measure anxiety (Spielberger et al., 1983), the Positive and Negative Affect Schedule (PANAS-SF) to measure general mood (Watson et al., 1988), the Perceived Stress Scale (PSS) to measure stress (Cohen et al., 1983), and the “Set, setting, and intention" questionnaire to map expectation (Haijen et al., 2018). These questionnaires are not analyzed in the present thesis due to the limited scope of the examined research question.

2.2.3 Setting

Participants received ketamine in a dark room in a hospital bed while covered in two to three blankets. They were also wearing eye shades most of the time and were instructed to be quiet during the continuous infusion of ketamine. Thus, participants kept their eyes closed for most of the induction, session, and subsequent emergence from the ketamine[2]. However, despite repeated instructions, some participants talked and kept their eyes open during the session. This was requested because eyes open tend to alter the spectral profile of EEG and increase the signal diversity relative to eyes closed, which might confound the potential effects (Farnes et al., 2020).

2.2.4 EEG

Following the initial questionnaires, a 64-channel EEG cap with active channels was mounted (actiCAP slim, Brain Products). Electrode contact with the scalp was adjusted with a soluble conductance gel, and contact quality was ensured by keeping impedance below 5kΩ. Prior to ketamine administration, we recorded two baseline resting-state spontaneous EEG activity for 5 minutes with eyes closed (EC) and eyes open (EO).

To avoid nausea and sickness after the end of the experiment, participants were instructed to fast for 6 hours, and avoid drinking for 2 hours before

[2]Even though participants were instructed to keep their eyes closed behinid the blindfold, some subjects might have kept their eyes open. Post-session interviews revealed that some participants didn’t know whether their eyes were closed or not due to the effect of ketamine on proprioception.

starting the ketamine session. Racemic ketamine (Ketalar®, Pfizer AS, Lysaker, Norway) was given to patients through a continuous intravenous infusion managed by an anesthesiologist. The infusion was delivered using a Braun infusion pump (Braun®). The participants received an initial bolus dose of ketamine around 9.1 mg/kg/h while counting out loud. When the participant stopped counting, the dose was gradually stabilized to around 1.5 mg/kg/h. Stabilizing the infusion rate when participants stopped counting ensures some degree of similarity in the individual effect of ketamine, at least on a behavioral level. On average, participants received a total dose of 125 mg/kg racemic ketamine over 35 minutes. The dose varied across participants to establish a dose-response relationship for the subsequent data analysis with a maximum permitted dose of 300 mg/kg. This amount is considered anesthetic and makes the participant unable to answer, making awakenings challenging. During stable infusion, we repeatedly aroused the subject (10 minutes between 'awakenings') by saying their name aloud and squeezing their trapezius muscle. When the subject responded to outside stimuli (e.g., by saying "yes?"), we asked them a series of questions (see 2.2.3). After the session, participants received Metoclopramide to prevent nausea, administered by the anesthesiologist.

2.2.5 Psychedelic and working memory assessment

Participants undergoing ketamine administration were awakened three or four times with 5-10 minutes of resting EEG between awakenings. They were asked about their recent experiences and whether they had experienced ego dissolution and unity with the universe. They completed a simple working memory task to ensure they understood the questions. No hints or feedback were provided during questioning. The infusion was stopped after four awakenings or an hour after the intervention began. Participants filled out questionnaires regarding their psychedelic experiences once the effects of ketamine had sufficiently washed out. The questionnaires included the Ego Dissolution Inventory (Nour et al., 2016), the Psychological Insight Scale (Peill et al., 2022), the Challenging Experiences Questionnaire (Barrett et al., 2016), and

the Mystical Experiences Questionnaire (Barrett et al., 2015). The MEQ involved a subjective estimate of the effect of ketamine, represented as a response graph with time on the x-axis and an estimated intensity of the psychedelic experience on the y-axis (see appendix 8.4).

2.3 Analysis

The analysis phase consisted of preprocessing the data, performing analyses, and visualizing the results.

2.3.1 EEG preprocessing

Preprocessing of EEG data consisted of two stages. This was done to avoid unnecessary polishing of EEG data. The preprocessing was performed using MNE with Python code in the Visual Studio Code editor (Massey, 2023).

In the first stage, we sliced and removed the EEG data during the awakenings due to artifacts and a lack of relevance to the research question. We then resampled the data to 500 Hz in accordance with Jing & Takigawa (2000). Following this, we created epochs and employed a high pass filter at 0.5 Hz in accordance with Winkler et al. (2015). The bad channels were also interpolated if they differed significantly from the normal activity for more than 75% of the duration of an entire recording. In this stage, the data was partly preprocessed and ready for a preliminary analysis that could later be compared with the fully preprocessed data.

This data proved highly noisy, so we decided to preprocess the data further to achieve a higher signal-to-noise ratio. For the rest of the preprocessing, we first applied a low-frequency filter at 45 Hz to remove power line noise and other high-frequency artifacts. Then we employed MNE's autoreject package to reject bad epochs and remaining bad channels (Jas et al., 2016; Jas et al., 2017). The data was then inspected and evaluated as less noisy. Lastly, we performed a re-referencing of electrodes, computed the average reference, and performed another

autoreject to remove residual noise. Our data became easier to interpret and compare, and because of this, we kept the more processed version.

2.3.2 Measures

To investigate whether there were any systematic changes in neural activity when subjects reported having experienced ego dissolution and not, we calculated spectral power in the canonical EEG bands and signal diversity through Lempel-Ziv complexity (Lempel & Ziv, 1974). Power spectral density was computed with the multitaper method and Lempel-Ziv complexity based on the original implementation of the algorithm (Lempel & Ziv, 1976). Both were implemented in Python 3.10, MNE 1.3.1, and pyconscious (Nilsen, 2020).

2.3.3 Statistical analysis

In order to test our hypotheses laid out in the introduction, the following includes detailed descriptions of every analysis performed. Since this is an exploratory study, we opted to test out a variety of information-processing measures described in the introduction.

2.3.4 Ego dissolution

Ego dissolution was computed by awakening binary scores into ego dissolution (ED) and non-ego dissolution (NED). EEG data were classified as ego dissolution if (1) the participant was receiving ketamine or still intoxicated, and (2) if they answered affirmatively to the question: “Did you lose your sense of who you were?". This question is inspired by the Ego-Dissolution Inventory (EDI) items: “I experienced a dissolution of my “self" or ego" and “I lost all sense of ego" (Nour et al., 2016). For non-ego dissolution, it is the same as the former, besides participants answering negatively to the ego dissolution question. It was assumed unlikely that the ego dissolution effect would occur before the ketamine administration, as in EC and EO, and probably not last over 30 minutes after ketamine

infusion cessation, as in the case of the emergence measure. Those who received ketamine infusions but did not answer affirmatively to the ego-dissolution question were also clustered in the non-ego dissolution data.

Both estimates were used to compute power spectral density (PSD) plots across conditions. The PSD was computed using MNE's psd multitaper function and manually clustered into alpha, beta, theta, and gamma power. For the expanded ego dissolution classification described above, we computed Robust ANOVAs to compare the difference in explained variance within each power band and between the ED items.

To test previous findings of increased signal complexity in spontaneous EEG data during ketamine (Farnes et al., 2020), we compute the Lempel-Ziv complexity. The Lempel-Ziv complexity measure is designed to quantify the unpredictability of the brain pattern. Thus, the lower the predictability, the higher complexity. We averaged across epochs, channels and conditions, which yielded a unique value for each participant. To compare the groups, we conducted an independent t-test because the samples had different sizes.

2.3.5 Ketamine

In this section, we repeated the previous statistical analyses for ego dissolution, but instead of comparing ED items, we compared sober versus ketamine-intoxicated states. Ketamine included all measures where we were certain the participant was intoxicated, and non-ketamine included only the eyes closed (EC) condition. We did not include induction or emergence in the non-ket condition because participants were slightly intoxicated during these measures. Moreover, the eyes open (EO) condition was excluded because it makes it more difficult to compare the ketamine state, in which participants' eyes were closed.

We then calculated the power spectral density (PSD), as in the ED analyses, and conducted an independent t-test to estimate whether there were any significant differences between the pairs across power bands.

We also computed the Lempel-Ziv complexity as before to test for differences in signal complexity across the two conditions. The Lempel-Ziv complexity measure is designed to quantify the unpredictability of the brain pattern. Thus, the higher the predictability, the higher complexity.

3 RESULTS

3.1 Ketamine versus baseline

3.1.1 Power spectral density

We computed the PSD of three conditions to inspect (see Figure 1) visually. These included ketamine (not including emergence and induction periods) and the two wakefulness conditions, eyes closed (EC) and eyes open (EO).

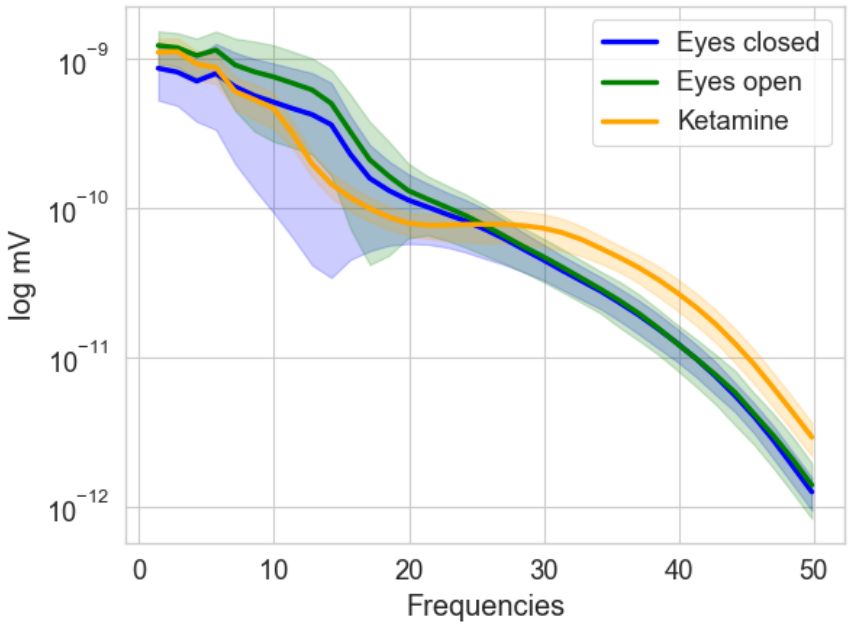

Figure 1: *The power spectral density distribution from 1 to 50 Hz between Ketamine and non-ketamine conditions. The shaded region was calculated by standard error mean times two.*

We performed independent t-tests to compare PSD across the wakefulness and ketamine conditions and found significant variations in alpha, t(2,17) = 2.33, p = .02, and gamma bands, t(2,17) = -2.18, p = .03, between the ketamine and eyes open condition (see Figure 2).significant mean difference between ketamine and eyes closed in the alpha power band, t(2,17) = 3.76, $p < .001$.

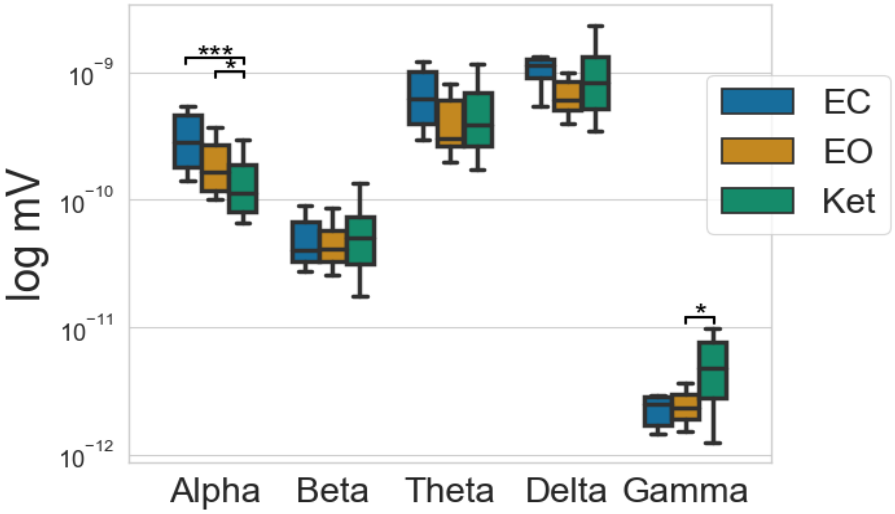

Figure 2: *Comparison of mean spectral power across wakeful conditions EC (eyes closed) and EO (eyes open) and continuous ketamine infusion (Ket).*

3.1.2 Lempel-Ziv complexity

We computed Lempel-Ziv complexity across the following conditions: eyes closed (EC), eyes open (EO), and ketamine (Ket). We found a significant mean difference between EC and ketamine, t(1,12) = -2.40, p = .03. Neither EC and EO, t(1,12) = 1.75, p = .10, nor EO and Ket, t(1,12) = -0.035, p = .97, were significant.

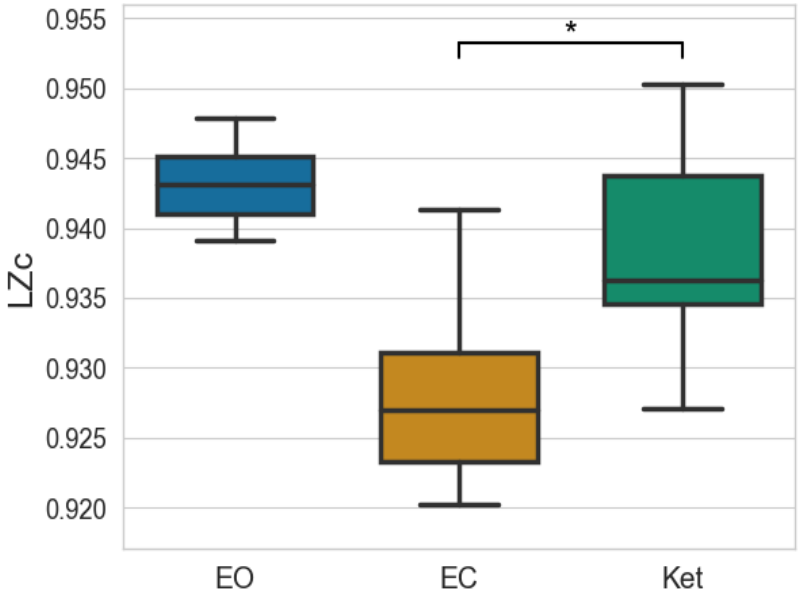

Figure 3: *Relationship between spontaneous EEG during wakefulness, eyes open (EO) and eyes closed (EC), and stable continuous ketamine sedation (Ket), $p < 0.05$.*

3.2 Ego dissolution vs. non-ego dissolution

3.2.1 Power spectral density

We computed the power spectral density (PSD) to investigate broad spectrum changes between periods of reported ego dissolution (ED) and non-ego dissolution (NED) (see Figure 1). Although no statistical tests were performed on these data points, it provides an overview of potential differences that might appear in the subsequent analyses.

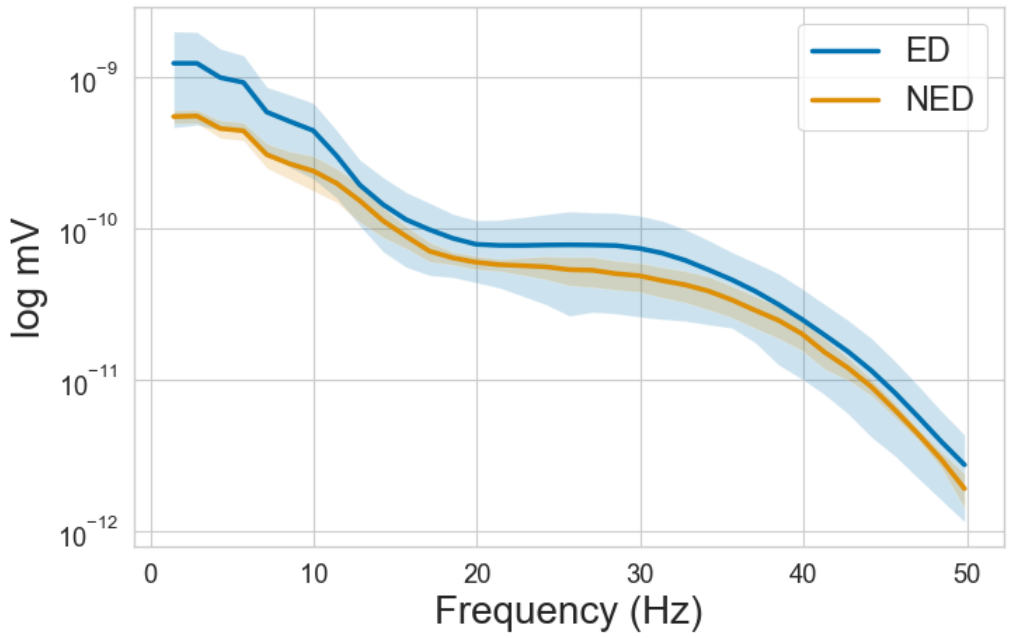

Figure 4: *illustrates the relationship between EEG power spectral density and periods where subjects reported experiencing ego dissolution (ED) vs. not (NED).*

Based on the PSD, we calculated the mean power within each canonical frequency band to quantify the difference between ED and NED. None of the power bands reached significance in t-tests, but ED demonstrated higher mean across all power bands besides alpha.

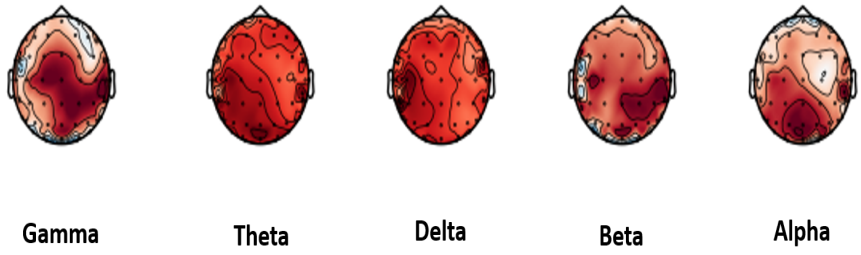

Figure 5: *Topographical difference plot between ego dissolution (ED) and non-ego dissolution (NED). Only plotted for exploratory reasons and visualization purposes.*

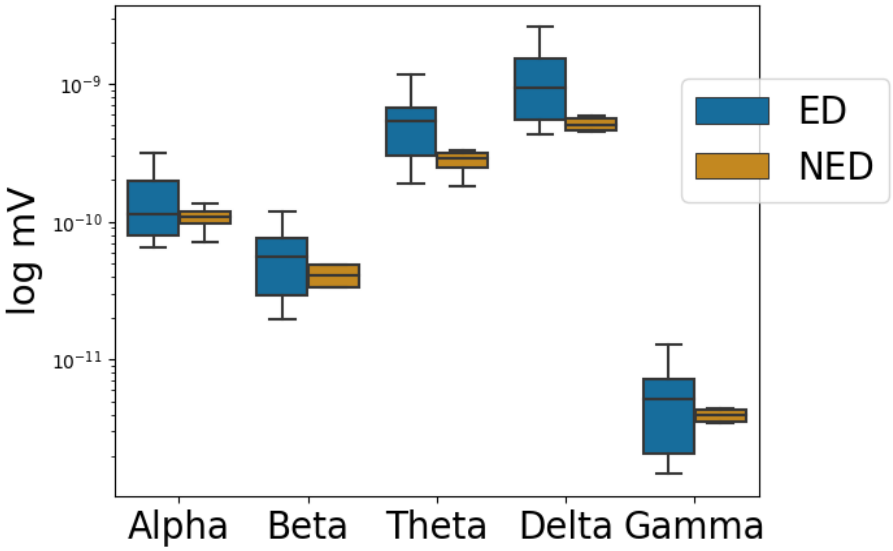

Figure 6: *Relationship between ego dissolution (ED) and non-ego dissolution (NED) in canonical bands*

In post hoc analyses, we computed the power difference between ED and NED to inspect potential power differences for the two conditions visually. To achieve this, we performed a t-test between the conditions for each electrode and created a topographical plot.

3.2.2 Lempel-Ziv complexity

Lempel-Ziv was computed for all ED and Non-ED conditions. An independent t-test was conducted because of the unequal sample size, and the results were insignificant, t(1,20) $= 0$, $p = 1.0$ (See figure 6).

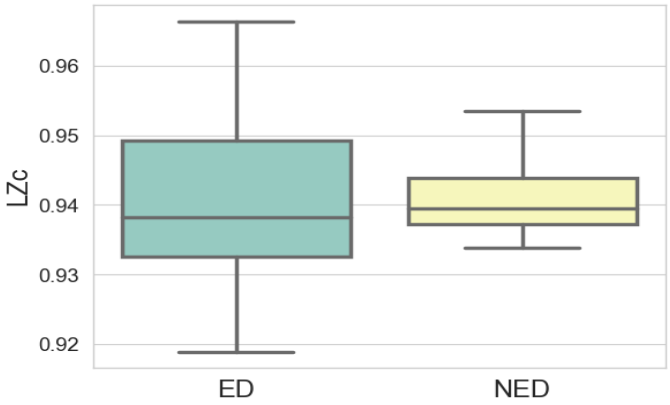

Figure 7: *The relationship between ego dissolution (ED) and non-ego dissolution (NED) in signal diversity measured by Lempel-Ziv complexity (LZc).*

4 DISCUSSION

4.1 Main findings

In this paper, we aimed to investigate potential EEG markers of ego dissolution (ED). To investigate this, we administered sub-anesthetic ketamine sedation to healthy participants in combination with an intermittent awakening paradigm. We observed that signal diversity (as measured by Lempel-Ziv complexity; LZc) increased from resting wakefulness with eyes closed, to ketamine sedation, in accordance with previous findings (Schartner et al., 2017; Farnes et al., 2020). While we did not achieve a significant decrease in LZc from wakefulness eyes-open resting condition to eyes closed, as predicted by previous studies (Farnes et al., 2020), the results trended in the same direction (see Figure 3). We also observed a significant decrease in alpha band power and a significant increase in gamma band power between ketamine and wakeful rest with eyes closed. Previous studies have found similar changes in alpha and power during continuous ketamine (Salle et al., 2016) and only in alpha power (Vlisides et al., 2018). Other studies have found

For periods of ketamine sedation where subjects retrospectively (during an intermittent awakening) reported that they had experienced ego dissolution relative to non-ego dissolution periods, we observed no clear relationship between the employed measures according to the initial hypothesis. Meanwhile, we observed overall increased mean field spectral power during reported ego dissolution compared to non-ego dissolution during continuous ketamine infusion. Currently, our results fail to support the hypothesis that ego dissolution can be detected by EEG quantified as power spectral density or signal diversity.

Our null-finding can be interpreted in two ways. First, there is simply no difference between measurable brain activity and phenomenology in EEG measures of ego dissolution. This goes somewhat against the predictive coding framework since some of their supporters believe that the efficacy of psychedelics partly stem from how ego dissolution induce potential change in unhealthy prior beliefs. Regardless of this, it might also mean

that ego dissolution is not a "special" state compared to other psychedelic states. This might explain why most studies ask participants about ego dissolution after the session is over instead of during the actual session. This makes some sense since it allows more clear thought and potentially more well-formulated descriptions of the experience. However, this makes the post-mortem accounts potentially less trustworthy, which could mean that there might simply be an effect of the psychedelic experience, not ego dissolution in particular. This is doubtful, however, as many studies have found correlations between ego dissolution in particular and treatment outcome. In the end, the literature is mixed and this issue needs to be explored explicitly in a dual design in the future to better understand the potential underlying causal mechanisms driving this difference in experience and measurement.

The other interpretation is that our study was unequipped to investigate the brain activity difference between the groups. This makes some sense, as we had skewed distributions towards ego dissolution compared with non-ego dissolution. This makes comparisons more difficult, but we found no mean difference which either means there are no real difference between these populations, or that our results were skewed because of small sample sizes. This makes it difficult to conclude anything concrete, but it is safe to say that more power and, thus, more accurate measures of these groups is necessary. Our results may also indicate that the ketamine dose we used was too high since almost all participants experienced ego dissolution.

To conclude, the current study results might either reflect no difference between ego dissolution and other psychedelic states - which might prompt a revision of the predictive coding framework - or we were unable to detect the difference because of skewed data and low power. These potential limitations are described in more detail below.

4.2 Limitations

4.2.1 Low sample size

The experimental sample in our study has limited the scope of the study as it provides less power to measure effects. This might also explain why some of our statistical tests did not achieve significance, such as the contrast between LZc during eyes open and eyes closed conditions. Low sample size can also increase the chance of type 2 errors, i.e., rejecting a true null hypothesis. Meanwhile, this study is technically demanding and time intensive rendering large sample sizes impractical given the scope of this thesis. Thus, this study is exploratory in nature.

4.2.2 Subjective report

While subjective reports are the gold standard for probing phenomenological experience, they might be unreliable in some scientific contexts. First, ketamine at intermediate doses has strong psychedelic effects and memory consolidation issues (Clifton et al., 2018). This means that in combination with an intermittent awakening paradigm, subjects might not be able to report accurately what they experienced. We attempted to control for this using a simple working memory task and semantic memory task (see appendix 8.4). We observed that subjects could perform these tasks, suggesting they could at least understand and respond to task instructions. Further, even if the reports are reliable, it's unclear when in the preceding recording the experience took place. If ego dissolution is an unstable and short-lasting state, then the time period analyzed might contain only a fraction of the desired state even if the whole epoch is labeled as ED or non-ED. In this sense, the binary classification of ego dissolution might be too over-simplified, making comparisons more difficult. In addition, we assume that participants understand the ego dissolution concept and are able to recognize it as an experience. To avoid potential expectation effects, we did not explain how they could conceptualize and detect it. It is also difficult to conceptualize an experience that is inherently non-conceptual in essence. Thus we might risk confusing participants in what

to “look for". The lack of instruction on exactly what an ego-dissolution state is might also be a potential limitation that might obscure the comparisons between ego dissolution and non-ego-dissolution EEG data, as some recordings might be mislabeled.

4.2.3 Heterogenous infusion rates

Given individual responsiveness to ketamine, infusion rates were individually adjusted. While this may increase variance in subjective effects, it also increases the variance in reported experiences. Given that it's difficult to titrate ketamine to a desired level beyond using rough bounds, we could not aim for an infusion rate that ensured a specific experience. Since the aim of the current study is to look for potential markers that can be used by clinicians, we varied the infusion rate computed against the degree of ego dissolution. This dose-response relationship was not computed in the current study, however.

4.2.4 Other issues

The following limitations are general issues that do not influence the interpretation of the results but provide potential issues that can be improved upon in subsequent studies.

4.2.5 Heterogeneity of measures

Another limitation is the lack of heterogeneity in the sample, making the findings difficult to generalize. Specifically, all the participants were healthy white males in their 20s and 30s of native Norwegian birth. This is an issue because clinical cases tend to be markedly more heterogeneous than the current experimental group. In addition, since they are suffering from a range of mental disorders, they might have very different neural markers than those found in the current study. Although attempts were made to collaborate with a Norwegian hospital that provides ketamine

treatment to their patients, this did not work out, and the study had to include healthy volunteers instead. Furthermore, since we used convenience sampling, we attempted to include both genders. Still, a majority that responded were male, and all those who could participate on the given dates were male. This is unfortunate since women are almost twice as likely to receive mental health treatment (Terlizzi & Zablotsky, 2020). However, it seems that treatment efficacy does not tend to vary by gender, according to a recent study (Freeman et al., 2019), which may provide some relief. Meanwhile, some have found higher CNS activation in female participants, as reflected in EEG data (Aslanyan et al., 2017), higher beta power for men, and higher alpha power in women (Corsi-Cebrera et al., 1993). Taken together, the homogeneity of the group probably restricts the generalizability of the results. On the other hand, a more homogenous sample reduces variation. Thus, if one fails to find conclusive support for the alternative hypothesis (H1), this strengthens H0 even more unless H1 is only valid for a specific sub-population. For instance, as a specific gender or patient population. This is considered unlikely as ego dissolution is a common phenomenon experienced by a heterogeneous group of subjects (source?).

4.2.6 Missing control group

The first potentially glaring limitation of this study is that it only contains the experimental condition, i.e., no placebo group. This is a problem because it limits the interpretation of our results to confounders. In addition, it makes it more challenging to label EEG data into, e.g., “Ket" and “Non-ket" because there is often an effect of expectancy, i.e., the placebo effect. Although we did not include a control group, we instead compared changes in the ketamine relative to the baseline measures eyes closed and eyes open. However, the repeated measures design is prone to other issues like the order effect, in which the measurement order influences the data collected (Godby, 2022). While it is more or less impossible to offer an effective placebo for a psychoactive compound, especially a placebo that could potentially induce a subjective state akin to ego dissolution, alternative control groups like meditation or other

anesthetics might be valid alternatives.

4.2.7 Clinical ketamine therapy practice

Another limitation of our study is the dose administered to the participants. Most ketamine therapy options administer 0.5 mg/kg over 40 minutes (source), while the current study administered on average 1.5 mg/kg/h ketamine over 30 minutes. Thus, the probability of ego dissolution is significantly lower in a clinical setting if the chance of experiencing ego dissolution is a function of dose. However, a high signal-to-noise ratio might make our ED model more accurate. This assumes that the ED-signal increases linearly with dosage. It might instead diffuse across more networks and become less pronounced as the dose increases.

4.2.8 Independent t-test for paired data

In our statistical tests, we could not perform the paired t-test because the grouped data were unequal. This is slightly problematic because, in most clinical settings, individual change is more important than expected grouped change. However, independent t-tests are more strict in comparing the two groups since it assumes independence compared to the paired t-test. This means our group-wise differences are more robust but might miss potential clinically significant differences.

4.2.9 Multiple comparisons

The current study was exploratory, which meant we employed many tests to look for differences between ego and non-ego dissolution. Multiple comparisons increase the probability of achieving significant results by chance (Benjamini, 2010). Given the number of tests we ran, this reinforces the null hypothesis despite the low sample size. The few significant comparisons, however, were all in accordance with previous studies.

4.3 Future work

Future work should investigate the clinical significance of ego dissolution in ketamine therapy, as this was beyond the scope of the current study. We also support a direct replication study with a larger, more heterogeneous sample size to see if the non-significant results persist with power spectral density and signal diversity as markers. They should also consider including functional connectivity within DMN and between SN and DMN as a marker in accordance with Carhart-Harris et al. (2012), Müller et al. (2018), and Carhart-Harris et al. (2013). Alternative markers for signal diversity could also be considered, although these tend to behave similarly between the different variants (Nilsen et al., 2020).

5 ACKNOWLEDGMENT

The current study was developed by André Sevenius Nilsen, Gernot Ernst, Birger Bang, and myself. Birger and I collected the EEG data at Kongsberg Hospital, and I performed the subsequent preprocessing and analyses of the data. The thesis was written by myself with feedback from André along the way.

I would like to thank my supervisor - André - for superb guidance and feedback throughout the project. To Birger Bang for the good company and excellent data collection help. To André Schjøth for the best of friendships and my mother for always having my back, even when I take the wrong turn. Lastly, I want to thank Kongsberg Hospital for their hospitality and their brilliant anesthesiologist, Gernot Ernst.

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7 SUPPLEMENTARY MATERIAL

7.1 Lempel-Ziv complexity between EC and ketamine

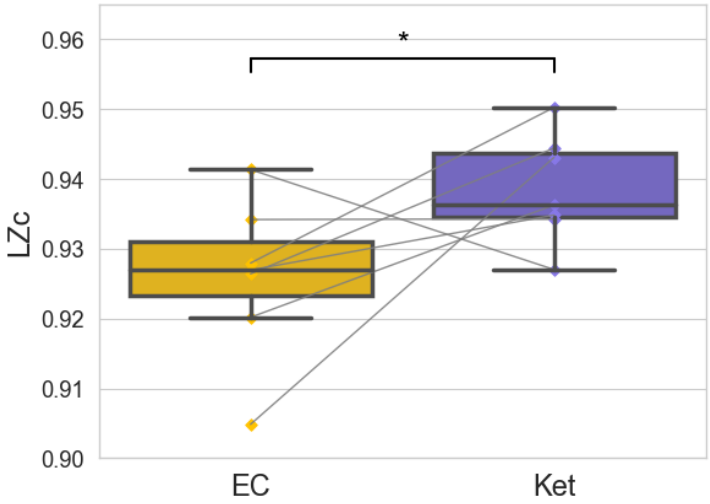

Figure 8: *Lempel-Ziv complexity between eyes closed (EC) and ketamine (Ket) with individual scatterplots and lineplot between the conditions. This was excluded because it did not provide much additional information to the original plot.*

7.2 Power spectral density between ED items

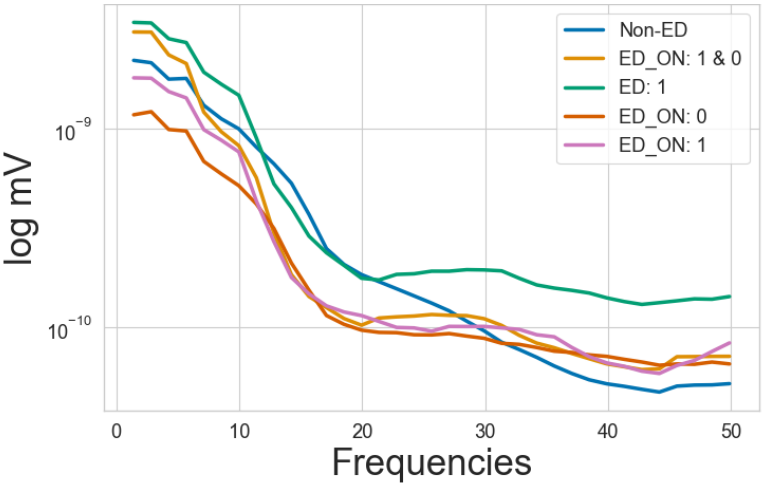

Figure 9: *Power spectral density between ED items. This was excluded because the differentiation of ego dissolution items seem unnecessary when the main objective of the current thesis is to detect ego dissolution, not its potentially overlapping distribution with oneness.*

7.3 Lempel-Ziv complexity between ED items

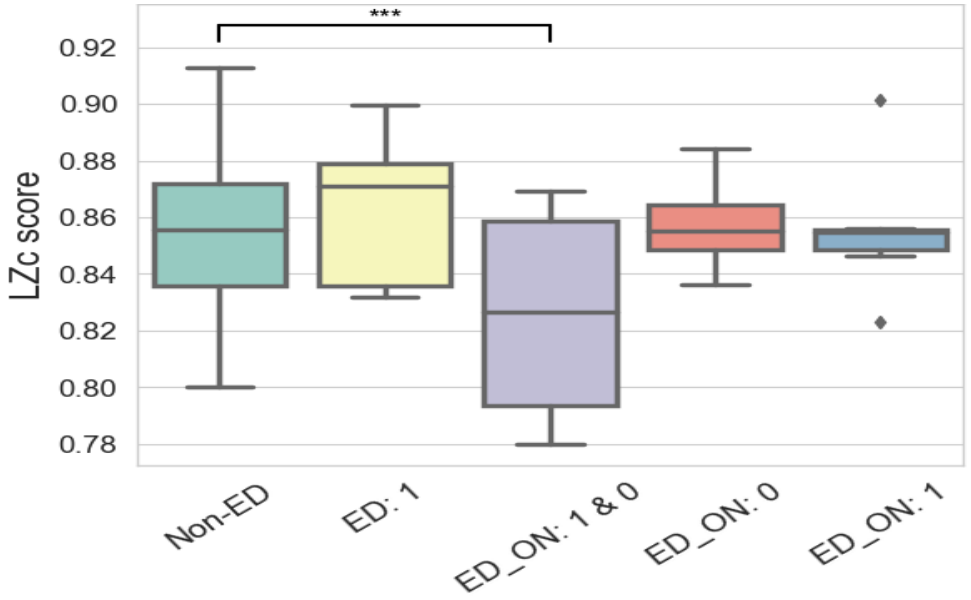

Figure 10: *Lempel-Ziv complexity between ED items. Non-ego dissolution: "Non-ED", ego dissolution: "ED", ego dissolution, no oneness (see appendix X): "ED_ON: 1 & 0", neither ego dissolution or oneness: "ED_ON: 0", and both ego dissolution and oneness: "ED_ ON: 1". This was excluded for the same reason as listed above.*

8 APPENDIX

8.1 Demographic questionnaire

- **Hva er ditt biologiske kjønn?**
- Mann
- Kvinne
- Annet:

  _____

Hva er ditt kjønn?

- Mann
- Kvinne
- Ikke-binært
- Annet:

  _____

Hva er din alder?
____år

Hva er din høyde?
____ cm

Hva er din vekt?
____kg

Røyker eller snuser du regelmessig? (minst én om dagen)

- Ja
- Nei

Har du spist noe før behandlingen?

- Ja

- Nei

Har du drukket kaffe før behandlingen?

- Ja
- Nei

Har du tatt noen medisiner eller rusmidler i løpet av de siste fem dagene?

- Ja

  Hvilke: _____

- Nei

Har du noen tidligere opplevelser med psykedeliske stoffer?

- Ja

  Hvilke: _____

- Nei

Har du hatt eller har en autoimmun sykdom?

- Ja
- Nei

Går du på cellegiftbehandling?

- Ja

  Nei

  itemize

8.2 Awakening questions

¨ Q1: What did you experience?

NOR: Hva opplevde du? (Siste opplevelse?)

¨ Q2: Did you experience anything [yes/no]?

NOR: Hadde du en opplevelse? [ja/nei]

¨ Q3**:** Did you lose your sense of who you were?

NOR: Mistet du følelsen av hvem du var?

¨ Q4**:** Did you feel at one with the universe?

NOR: Følte du deg i ett med universet?

¨ Q5: Remember these five words: ['house', 'cake', 'ball', 'cup', 'hat']. Which five words did I say?

NOR: Husk disse fem ordene: ['hus', 'kake', 'ball', 'kopp', 'hatt']. Hvilke fem ord sa jeg?

¨ Q6: I will name six cities. Answer the country if you know, answer 'next' otherwise:

NOR: Jeg vil navngi seks byer. Svar landet den tilhører hvis du vet, svar 'neste' ellers:

max width=

a) ['Moscow']	a)
b) ['Sevit']	b)
c) ['Dublin']	c)
d) ['Madrid']	d)
e) ['Botvel']	e)
f) ['Tierchi']	f)

recording of sedated spontaneous EEG (5 min), TMS-EEG (10 min) and spontaneous EEG (1 min), followed by awakening and report (1-5 min)

¨ Q1: What did you experience?

NOR: Hva opplevde du? (Siste opplevelse?)

¨ Q2: Did you experience anything [yes/no]?

NOR: Hadde du en opplevelse? [ja/nei]

¨ Q3**:** Did you lose your sense of who you were?

NOR: Mistet du følelsen av hvem du var?

¨ Q4**:** Did you feel at one with the universe?

NOR: Følte du deg i ett med universet?

¨ Q5: Remember these five words: ['house', 'cake', 'ball', 'cup', 'hat']. Which five words did I say?

NOR: Husk disse fem ordene: ['hus', 'kake', 'ball', 'kopp', 'hatt']. Hvilke fem ord sa jeg?

¨ Q6: I will name six cities. Answer the country if you know, answer 'next' otherwise:

NOR: Jeg vil navngi seks byer. Svar landet den tilhører hvis du vet, svar 'neste' ellers:

max width=

a) ['Warsaw']	a)
b) ['Barnesfort']	b)
c) ['Bretta']	c)
d) ['Copenhagen']	d)
e) ['Nemessa']	e)
f) ['London']	f)

¨ Q7: What smell is this?

NOR: Hvilken lukt er dette?

2nd recording of sedated spontaneous EEG (5 min), TMS-EEG (10 min) and spontaneous EEG (1 min), followed by awakening and report (1-5 min)

¨ **Q1:** What did you experience?

NOR: Hva opplevde du? (Siste opplevelse?)

¨ **Q2:** Did you experience anything [yes/no]?

NOR: Hadde du en opplevelse? [ja/nei]

¨ **Q3:** Did you lose your sense of who you were?

NOR: Mistet du følelsen av hvem du var?

¨ **Q4:** Did you feel at one with the universe?

NOR: Følte du deg i ett med universet?

¨ **Q5:** Remember these five words: ['dog', 'car', 'pen', 'chair', 'soup']. Which five words did I say?

NOR: Husk disse fem ordene: ['hund', 'bil', 'penn', 'stol', 'suppe']. Hvilke fem ord sa jeg?

¨ **Q6:** I will name six cities. Answer the country if you know, answer 'next' otherwise:

NOR: Jeg vil navngi seks byer. Svar landet den tilhører hvis du vet, svar 'neste' ellers:

max width=

a) ['Stalpor']	a)
b) ['Paris']	b)
c) ['Berlin']	c)
d) ['Enton']	d)
e) ['Stocholm']	e)
f) ['Chevesic']	f)

¨ **Q7:** What smell is this?

NOR: Hvilken lukt er dette?

3rd recording of sedated spontaneous EEG (5 min), TMS-EEG (10 min) and spontaneous EEG (1 min), followed by awakening and report (1-5 min)

¨ **Q1:** What did you experience?

NOR: Hva opplevde du? (Siste opplevelse?)

¨ **Q2:** Did you experience anything [yes/no]?

NOR: Hadde du en opplevelse? [ja/nei]

¨ **Q3:** Did you lose your sense of who you were?

NOR: Mistet du følelsen av hvem du var?

¨ **Q4:** Did you feel at one with the universe?

NOR: Følte du deg i ett med universet?

¨ **Q5:** Remember these five words: ['stick', 'fish', 'bag', 'ring', 'board']. Which five words did I say?

NOR: Husk disse fem ordene: ['pinne', 'fisk', 'bag', 'ring', 'brett']. Hvilke fem ord sa jeg?

¨ **Q6:** I will name six cities. Answer the country if you know, answer 'next' otherwise:

NOR: Jeg vil navngi seks byer. Svar landet den tilhører hvis du vet, svar 'neste' ellers:

max width=

a) ['Wien/Vienna']	a)
b) ['Rome']	b)
c) ['Bistup']	c)
d) ['Stocklin']	d)
e) ['Amsterdam']	e)
f) ['Mowec']	f)

¨ **Q7:** What smell is this?

NOR: Hvilken lukt er dette?

recording of sedated spontaneous EEG (5 min), TMS-EEG (10 min) and spontaneous EEG (1 min), followed by awakening and report (1-5 min)

¨ **Q1:** What did you experience?

NOR: Hva opplevde du? (Siste opplevelse?)

¨ **Q2:** Did you experience anything [yes/no]?

NOR: Hadde du en opplevelse? [ja/nei]

¨ **Q3:** Did you lose your sense of who you were?

NOR: Mistet du følelsen av hvem du var?

¨ **Q4:** Did you feel at one with the universe?

NOR: Følte du deg i ett med universet?

¨ **Q5:** Remember these five words: ['stick', 'fish', 'bag', 'ring', 'board']. Which five words did I say?

NOR: Husk disse fem ordene: ['katt', 'gutt', 'mopp', 'tre', 'bok"]. Hvilke fem ord sa jeg?

¨ **Q6:** I will name six cities. Answer the country if you know, answer 'next' otherwise:

NOR: Jeg vil navngi seks byer. Svar landet den tilhører hvis du vet, svar 'neste' ellers:

a) ['Firenze/Florence]	a)
b) ['Bern']	b)
c) ['Atolla"]	c)
d) ['Aarhus']	d)
e) ['Akham']	e)
f) ['Bergen']	f)

¨ **Q7:** What smell is this?

NOR: Hvilken lukt er dette?

Emergence from ketamine sedation (15-30 min)

¨ Q7. Can you tell us about your experiences during anesthesia?

NOR: Kan du fortelle oss om dine opplevelser under anestesi?

¨ Q8. Do you remember anything related to the experiment itself?

NOR: Husker du noe i forbindelse med eksperimentet i seg selv?

¨ Q9. Do you remember any dreams?

NOR: Husker du noen drømmer?

¨ Q10. What was the last thing you remember before falling asleep (and what is the last number you remember)?

NOR: Hva er det siste du husker før du sovnet (og hva er det siste tallet du husker å ha telt opp til)?

¨ Q11. Anything else?

NOR: Noe annet?

¨ Q12. Which of these odors did you smell just before emerging from propofol sedation [presented with five different odors]?

NOR: Hvilke av disse luktene husker du å ha luktet rett før å ha blitt vekket opp fra sedasjon med propofol [presenteres med fem forskjellige lukter]?

8.3 Set, setting and intention, Norwegian translated version

De følgende spørsmålene er rettet mot din instilling og forventning til behandlingsopplevelsen. Svar ved å krysse av på linjen hvor enig eller uenig du er i påstandene.

Jeg føler meg komfortabel med den kommende opplevelsen.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg føler meg åpen for den kommende opplevelsen.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg føler meg godt forberedt på den kommende opplevelsen.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg føler meg engstelig.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg er i godt humør.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg føler meg klar til å overgi meg til det som måtte skje.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg er overopptatt av arbeid mitt og/eller mine livsoppgaver.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg har en god følelse om forholdet mitt til de som vil være med meg under opplevelsen.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg har et godt forhold til hovedpersonen/personene som skal passe på meg under den kommende opplevelsen.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Omgivelsene/settingen føles bra for min kommende opplevelse.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg har sterke forventninger til den kommende opplevelsen.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

Jeg har en klar intensjon for den kommende opplevelsen.

|————|————|————|————|————|————|————|————|

0: helt uenig helt enig: 100

8.4 Subjective response curve

Vennligst angi den subjektive responsen (opplevd intensitet) du hadde på ketamin i dette koordinatsystemet. "0" representerer tidspunktet for starten av infusjonen/behandlingen.