# Prosjekttittel: *Ketamin mot depresjon: fenomenologi og nevrale korrelater*.

Scientific title: S*ubjective phenomenology of patients receiving ketamine-infusions as treatment against treatment resistant depression and their electroencephalographic neural correlates; outcome- and experiential effects of set in a clinical setting.*

Project leader: Carsten Bundt, PhD.

Project plan:

## Purpose:

The purpose of this project is to investigate how the clinical outcome following ketamine infusion treatment against treatment-resistant depression is associated with patients’ 1) pre-treatment psychological state, 2) properties of conscious experience during the ketamine infusion, and 3) properties of brain activity during the treatment.

## Background:

Depression is a condition that is hard to treat with both therapy and the standard psychiatric medical interventions; up to two thirds of patients do not respond to the first antidepressant medication and up to 1 third do not respond to multiple interventions, leaving them eligible for a treatment resistant depression diagnosis (TRD) [(Little, 2009)](https://paperpile.com/c/xAKbb0/5SYF).Treatment resistant depression is an immense cost to society, and to the individual patients [(Johnston et al., 2019)](https://paperpile.com/c/xAKbb0/gRbx), with up to a third attempting suicide during their life [(Bergfeld et al., 2018)](https://paperpile.com/c/xAKbb0/VAmu).

A novel and promising treatment for depression is the administration of psychedelics like ayahuasca, psilocybin and lysergic acid diethylamide, often in combination with therapy [(Muttoni et al., 2019)](https://paperpile.com/c/xAKbb0/1Y7B). Due to legal status, these psychedelics are not as widely studied as the psychoactive drug ketamine, which is normally used as an anaesthetic [(Li & Vlisides, 2016)](https://paperpile.com/c/xAKbb0/oF1L).

Ketamine has been shown to have fast-acting antidepressant effects when used in lower dosages, with a recent review finding Ketamine to have a strong antidepressant effect 4 hours after administration (77%) and medium effect 72 hours after treatment (43%) [(Katalinic et al., 2013](https://paperpile.com/c/xAKbb0/rz2B)).In addition, as ketamine has been used extensively for clinical purposes, its safety is well documented (Hyde, 2015), making it a strong candidate for psychedelic therapy against depression. In fact, the usage of ketamine for this exact purpose has become widespread in the last decades, at both the private and public level [(Jennings et al., 2011)](https://paperpile.com/c/xAKbb0/CzJb).

However, the mechanism behind the antidepressant effect of ketamine is debated, regarding neuroplasticity (e.g. BDNF, mTOR, AMPA and NMDA [(Matveychuk et al., 2020)](https://paperpile.com/c/xAKbb0/OUhr)) and cognitive models (e.g. REBUS [(Carhart-Harris & Friston, 2019)](https://paperpile.com/c/xAKbb0/zu2p)), pharmacology (e.g. [(Hashimoto, 2020)](https://paperpile.com/c/xAKbb0/Mimz)), to the phenomenology of the psychedelic experience itself ([Ballard & Zarate, 2020](https://paperpile.com/c/xAKbb0/8OzZ); [Yaden & Griffiths, 2021](https://paperpile.com/c/xAKbb0/VQ2K)). Specifically, the phenomenology of the psychedelic experience is of interest as it constitutes a 'complicating' factor of treatment in that it is sensitive to prior experiences and associations with the substance, and seems to be sensitive to the ketamine dose (Hyde, 2015). Furthermore, while some patients describe the changes in phenomenology as pleasant, they are described by others as unpleasant and sometimes so adverse that treatment is stopped [(Griffiths et al., 2021)](https://paperpile.com/c/xAKbb0/VqRP). On the other hand, if the psychotomimetic experience is not an important factor for positive treatment outcome, then that broadens the potential use cases for ketamine as an antidepressant (e.g. administered in conjunction with other anaesthetics, at home in smaller doses, or using protocols minimising such experiences).In summary, clarifying the role of the psychedelic experience induced by ketamine in treatment outcome of treatment resistant depression can have major implications for clinical guidelines and research.

While the therapeutic effect of ‘classical’ psychedelics (ayahuasca, psilocybin, and lysergic acid diethylamide) have been observed to be influenced by the psychedelic experience itself [(Kadriu et al., 2021)](https://paperpile.com/c/xAKbb0/Ygvu), the link between the phenomenological effects of ketamine and the antidepressant effects is not as well defined. However, some studies have looked into the efficiency of S-ketamine and the subjective measures of dissociation. A case-report study with two participants both receiving S-ketamine and one week later, racemic ketamine, found that the first participant responded equally well to both ketamine versions, while the other participant did not respond well to either [(Paul et al., 2009)](https://paperpile.com/c/xAKbb0/hA5B). Another study with four participants receiving S-ketamine had a 50% response rate and no dissociative effects [(Paslakis et al., 2010)](https://paperpile.com/c/xAKbb0/kHSY). At the same time, other studies have noted strong dissociative effects and comparable response rates after ketamine infusion [(Denk et al., 2011)](https://paperpile.com/c/xAKbb0/atFF); [(Segmiller et al., 2013)](https://paperpile.com/c/xAKbb0/qFrn). One recent report found a greater antidepressant effect for people who reported relatively larger alterations in phenomenology [(Sumner et al., 2021)](https://paperpile.com/c/xAKbb0/n8VP), although experiencing anxiety when undergoing ketamine infusions against depression is associated with negative treatment outcome [(Aust et al., 2019)](https://paperpile.com/c/xAKbb0/1d0L). On the other hand, studies on the antidepressant effect of ketamine involving concurrent administration of anaesthetics like propofol, which are highly amnesic, also show effect, albeit short lasting [(Hyde, 2015)](https://paperpile.com/c/xAKbb0/Sq62). Other studies do not show an antidepressant effect of intraoperative ketamine administration [(Mashour et al., 2018)](https://paperpile.com/c/xAKbb0/35j1).

Together, these results indicate that the relation between antidepressant effects and psychedelic experience is complicated and needs to be understood better. A better understanding may then facilitate therapy/dosage/setting to maximise therapeutic effect, minimise adverse effects, and to possibly find a way to simplify the procedure so that ketamine therapy can be done in a wider range of clinical settings or at home. Similarly, if the psychotomimetic experience is of importance, it also opens questions on how the experience can be modulated. While the intensity of the experience is heavily modulated by the exact dosage of ketamine administered, and possibly other factors, it can also vary from session to session and patient to patient, for the same dose. For instance, Lai et al. [(2014)](https://paperpile.com/c/xAKbb0/CHBt) and [(Loo et al., 2016)](https://paperpile.com/c/xAKbb0/Pp90) found increased ketamine doses to induce increased dissociative effects, but Cusin et al. [(2017)](https://paperpile.com/c/xAKbb0/uD5u) found that dissociative symptoms *decreased* by higher ketamine doses. Based on this, it seems reasonable to conclude that there are more factors working to influence each session than just the molecule itself.

Further, valence of the experience might be influenced by outside factors like the patient's current mood and stress, also termed the patient’s ‘mindset’. If valence of experience is a predictor for treatment outcome and/or desire to continue treatment, then this is important to know so it can be controlled for or modulated. For example, the normal functioning of the HPA-axis, which is involved in stress responses, is often altered in depressed patients who may exhibit atypical cortisol regulation [(Markopoulou et al., 2009)](https://paperpile.com/c/xAKbb0/zJPe). Ketamine is found to rapidly increase endogenous cortisol production that interacts with the individual’s circadian rhythm [(Khalili-Mahani et al., 2015)](https://paperpile.com/c/xAKbb0/hqBj). Thus, cortisol levels prior to treatment might be an interesting biological and physiological marker of treatment experience or outcome.

Further, while pre-treatment mindset and overall stress can be modulated prior to treatment, any effect on experience can only be investigated after the treatment sessions are complete. For this reason, it is potentially valuable to find ways to monitor the intensity or depth of experience during treatment itself. One non-invasive method that suits this function well is electroencephalography (EEG), which is already used for similar clinical purposes such as anaesthesia monitoring. If depth and/or specifics of the experience can be monitored live by EEG, this opens up for titration of ketamine accordingly.

Some previous studies have shown that EEG can detect the experienced psychedelic effect of ketamine. For example, signal diversity of EEG has been observed to increase during sub-anesthetic levels of ketamine [(Schartner et al., 2017)](https://paperpile.com/c/xAKbb0/u2zg), and vary with the psychedelic experience itself [(Farnes et al., 2020)](https://paperpile.com/c/xAKbb0/kybG). Among the experiences, individuals receiving ketamine frequently report experiences of dissociation, disembodiment and ego transcendence; phenomenological changes which have been associated with reduction of alpha power in the precuneus and temporal-parietal junction [(Vlisides et al., 2018)](https://paperpile.com/c/xAKbb0/nTez). While mapping types of psychedelic experience with specific EEG markers is an ongoing question, finding such markers might not only be interesting from a scientific viewpoint, but also be important in clinical terms.

In sum, what influences experience is important to understand because it can guide future therapy in terms of what should be emphasised. For instance, if experience is irrelevant, then clinicians should strive to reduce the uncomfortable parts by potentially administering ketamine in adjunction with other anaesthetics, seek alternatives with similar mechanisms that do not induce potentially adverse experiences, or allow increased freedom in clinical treatment plans. On the other hand, if the psychedelic experience is important, it becomes crucial to understand what aspects of the experience are relevant, and how to update therapeutic guidelines accordingly.

## Goals and research questions:

Our goal is 1) to investigate the relationship between patients’ psychological and physiological state prior to treatment with sub-anesthetic doses of ketamine and outcome of treatment, including the experience of treatment, and, 2) investigate whether it is possible to monitor aspects of the psychedelic experience that might be indicative of positive treatment outcome using EEG-based measures.

We hypothesise that the patient's psychological and physiological state prior to treatment will affect their experience of the treatment, and that the experience of dissociation and ego-dissolution is correlated with better treatment outcome. We also hypothesise that EEG-based measures such as signal diversity and frequency band power can track depth of psychedelic experience. Finally, we hypothesise that there might be interactions between pre-treatment levels of cortisol, changes in cortisol levels released following the treatment and the treatment outcome.

## Material:

Study subjects are patients with treatment resistant depression who are scheduled to receive ketamine at DPS Nordre Østfold, an outpatient clinical service in Moss. These patients are scheduled to receive treatment independently of the planned research project. As in agreement with Sykehuset Østfold, the outlined project will be conducted to minimise time consumption, intrusion, and inconvenience for hospital staff, and patients. We aim for an initial sample size of N=10 patients having their first treatment and N=10 patients that have recently begun treatment. Given the current estimates of the positive outcome of ketamine treatment for depression, we expect ~50% of participants to have a positive outcome [(Krystal et al., 2019)](https://paperpile.com/c/xAKbb0/XTJ3). A sample size of minimum N=20 will allow initial comparisons of the relevant EEG-markers and pre-treatment variables of interest. Further data collection might be applied for at a later date due to possible confounding factors. While we ideally want patients who are naïve to the effects of ketamine (or any psychedelics) to control for confounding factors relevant when investigating phenomenological experience, this will likely be limited by the available population of patients about to receive, or who are receiving, treatment at DPS Nordre Østfold.

Each subject will be assessed one time, preferentially at the time of their first treatment with ketamine. Outcome measures, such as depressive symptoms in the following weeks, will be provided by the hospital in an de-identified fashion, aiming to preserve the anonymity of the subjects.

## Inclusion criteria

Patients who are going to start, recently started, or are currently receiving ketamine treatment at DPS Nordre Østfold.

## Exclusion criteria

There are no exclusion criterias beyond those for being eligible for ketamine treatment.

## Methods:

We have designed this study based on the schedule of the hospital with the goal of reducing inconvenience for the patients and hospital employees. We will therefore be performing most of the work ourselves besides the IV infusion, which is performed by the medical personnel at Sykehuset Østfold.

To understand the mindset of the patients prior to the treatment onset, we will be using questionnaires. For current anxiety levels, STAI-5 short form [(Zsido et al., 2020)](https://paperpile.com/c/xAKbb0/U692) is fitting because it consists of the essential aspects of relevant anxiety items prior to the treatment. For the expectations, we will be using Haijen et al.’s [(Haijen et al., 2018)](https://paperpile.com/c/xAKbb0/IMPc) “set, setting & clear intentions” questionnaire as this is one of the few questionnaires developed to measure relevant aspects prior to a psychedelic experience. To measure the depression levels, we will use the MADRS [(Montgomery & Asberg, 1979)](https://paperpile.com/c/xAKbb0/bTKV) as it is a well established measure of depression. Lastly, to capture the circadian rhythm to match with the cortisol levels, the BALM questionnaire [(Brown, 1993)](https://paperpile.com/c/xAKbb0/q4DP) will be used.

The cortisol measures will occur once before treatment and once two hours later by saliva sample. We are measuring around 2 hours later because this is when the cortisol normally peaks (Khalili-Mahani et al., 2015). Because of this measurement, we will ask the participants not to consume any caloric food or drinks until the end of the experiment.

For the brain activity measurements, we will use a 64-electrode EEG cap with active electrodes, connected to a laptop with EEG recording software. The recordings will be done passively, that is, only the clinical personnel will be present with the patient during the whole treatment session.

After the treatment, we will assess their phenomenological experience with questionnaires designed to capture psychedelic experiences. To categorise the mysticalness of the experience, we will give the participants the Mystical Experience Questionnaire (MEQ)[(Barrett et al., 2015)](https://paperpile.com/c/xAKbb0/gLYj) to capture For breakthrough experiences, the Psychological Insight Scale (PIS) [(Peill et al., 2022)](https://paperpile.com/c/xAKbb0/MxuH) and Emotional Breakthrough Inventory (EBI) [(Roseman et al., 2019)](https://paperpile.com/c/xAKbb0/lTPA) fits well. For ego dissolution (e.g. ego death) we will use the Ego Dissolution Inventory (EDI) [(Nour et al., 2016)](https://paperpile.com/c/xAKbb0/w66B). To capture how challenging the experience was, we will employ the Challenging Experiences Questionnaire (CEQ) [(Barrett et al., 2016)](https://paperpile.com/c/xAKbb0/krx6). Finally, we will ask the patients to draw a subjective response curve, indicating the perceived intensity of the experience over time.

| Before Treatment: 1 h | During Treatment:  1 h | After Treatment:  1 h | Later: |
| --- | --- | --- | --- |
| Questionnaires:  Demographics, MADRS, PANAS, Perceived Stress Scale (PSS), STAI-5 - short form, “Set & Setting” (Haijen et al., 2018),  Basic Language Morningness Scale. | IV-infusion of ketamine administered according to clinical guidelines. | Questionnaires:  Ego Dissolution Inventory (EDI), Mystical Experiences Questionnaire (MEQ), Psychological Insight Scale (PIS), Challenging Experience Questionnaire (CEQ), Emotional Breakthrough Inventory (EBI).  Other measures:  Subjective response curve | Access de-identified outcome measures collected by the hospital. |
| Prepare EEG, record baseline (5 minutes eyes open and 5 minutes eyes closed) | Record EEG | Clean up EEG |  |
| Saliva sample at standardised time. |  | Saliva sample 2h after infusion onset. |  |

## Feasibility:

The prospect of finding effects is increased by the fact that the research project is concerned with multiple hypotheses and measurements. As the list of possible subjects is limited by the hospital's capacity and intake schedule, the risk of being underpowered in parts of the analysis is considerable. To increase statistical power, the subjects will be used as their own control for both the cortisol and EEG analysis by comparing baseline levels and activity recorded during treatment. While the study is exploratory in nature with the primary goal to guide further research, the size of the sample is sufficient to reveal strong to medium sized effects. In a situation where the analysis reveals clear trends of effect but without sufficient power for statistical significance, the addition of more subjects will be considered. If that occurs we will update the REK application.

## Estimated time frame:

Start of project: 1/6/2022

End of project: 1/7/2023

## Treatment of health information:

No additional health information is to be accessed than those collected by the experimenters and the outcome measures collected by the hospital. All data gathered by us will be stored locally in an deidentified fashion using an ID key that the hospital possesses. The outcome measures will similarly be accessed through the ID key managed by the hospital.

All health information is de-identified. Data might later be shared with institutional collaborators in Europe (Milan and Liege university), or shared in databases for open science. No identifying information will be shared. Locally, all data will be stored on either a server only accessible to the main researchers or locally on a password protected computer.

## Biological samples:

Saliva samples are to be collected on site in plastic tubes. They will be stored in water/ice containers until the end of the session, then transferred to -80 degree freezers. These will be marked with anonymous identification keys only, and stored in a secure freezer at the faculty of medicine, UiO. We will perform cortisol level analysis using the ELISA assay kit, and analyse inflammatory/anti-inflammatory cytokine gene expression using QPCR. The QPCR transcription process is done on partial genetic material and is thus insufficient in terms of identification, genetic tracing, or similar. The QPCR test is for the purpose of controlling for the presence of inflammatory cytokines which have been implicated in depression severity [(Zhan et al., 2020)](https://paperpile.com/c/xAKbb0/V1Oi). The samples will be analysed as soon as possible after acquisition, and within two months at the most. Following analysis, these samples will be destroyed, and thus not stored long-term in a biobank. Attila Szabo, PhD., will be responsible for the storage of the saliva samples at the medical faculty, UiO.

## Ethical considerations:

The addition of the research will be of no direct benefit to the patients, except the possibility of increased reflection upon own experience and its connection to the outcome. However, the research may lead to advantages in the form of increased knowledge of the interaction between psychological state, stress-levels, phenomenology and outcome of treatment. This may in turn lead to improved treatment procedures for the advantage of the group of TR-D patients in general, and perhaps also other clinical groups.

The research is non-invasive and builds upon a preexisting treatment procedure. As such, it inflicts minimal risk for the individual patient. There are however some minor inconveniences for the patients. For instance, there is potential for some discomfort when fitting the EEG cap before treatment and some inconvenience as they will have to clean their hair for water soluble electroconductive gel afterwards. Another inconvenience for the patients is that they will have to spend an extra hour at the hospital on the day of treatment. This will amount to around three hours in total of no eating for the participants. They will, however, be offered a sweet bun or something similar after the experiment is over to compensate for the low blood sugar.

Overall, we consider the experiment to be safe as we use well-proven non-invasive methods in a safe context. The disadvantages that patients may experience are primarily related to time, fatigue and discomfort, but there are no direct dangers in participating in the research. Ketamine is administered regardless of the research project, and in an established clinical setting, we assume that the additional measures will not have any significant negative impact on the treatment. Thus, we argue that the benefits of scientific progress and clinical validation of the treatment method outweigh the disadvantages to the individual patient.

## Financial sources:

The project receives no funding. All data collection will be done on a voluntary basis by two master’s students, as part of their thesis.

## Plan for publishing of results:

The primary goal of publishing is as two individual Master theses in Cognitive Neuroscience at the Institute of Psychology, University of Oslo. Subsequently, the results will be written up in one or more articles suitable for scientific publishing in international scientific journals.

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