

**SAMARBEIDSAVTALE**

*(Denne malen skal brukes I tilfeller hvor UiO samarbeider med en ekstern part i et forskningsprosjekt)*

mellom

**Universitetet i Oslo, [971 035 854]** -“UiO”

**ved/ (navn på prosjektets administrative enhet)**

og

**Østfold sykehus, [698 60 000]** – “Partner”

**ved/ DPS Nordre Østfold**

(UiO og Partner i fellesskap er videre omtalt som “Partene”)

1. **Introduksjon**

Denne samarbeidsavtalen – heretter omtalt som «Avtalen» - regulerer rettighetene og forpliktelsene til Partene i aktuelle prosjekt: *(prosjektnavn, prosjektnummer)* – heretter omtalt som “Prosjektet”.

De følgende vedlagte dokumenter skal være inntatt som en del av Avtalen:

Vedlegg 1: Prosjektbeskrivelse

Vedlegg 2: Årsbudsjett

Vedlegg 3: Relevant Prosjektbakgrunn tilført Prosjektet av Partene.

1. **Definisjoner**

Prosjektbakgrunn Materielle bidrag, immaterielle rettigheter eller ekspertise/know-how som en part tilfører til Prosjektet. Prosjektbakgrunnen som er tilført av den enkelte part i Prosjektet er spesifisert i vedlegg 3.

Kommersiell utnyttelse Direkte eller indirekte bruk av prosjektresultater i utviklingen eller markedsføringen av produkter, tjenester eller prosesser basert på prosjektresultater. Overføring og/eller lisensiering av bruk av prosjektresultater til tredjeparter, med unntak av publisering i samsvar med seksjon 5.3.

Immaterielle rettigheter Alle rettigheter til tekniske løsninger, metoder, prosesser og prosedyrer, uavhengig av om disse er, ikke er, vil bli, eller ikke vil bli patenterte. Alle opphavsretter og rettigheter til varemerker, kjennetegn, design, plantearter, databaser, kretsmønstre for integrerte kretser, illustrasjoner, spesifikasjoner, prototype, forretningshemmeligheter og lignende.

Prosjektresultater Forskningsresultater produsert eller oppnådd i forbindelse med Prosjektet, herunder immaterielle rettigheter, uavhengig av om resultatene har eller kan få et rettslig vern.

Prosjektperiode Tidsperioden som Prosjektet skal utføres i, som spesifisert i vedlegg 1.

1. **Forpliktelser** 
   1. **Gjennomføring av Prosjektet**

Partene er pålagte å utføre oppgavene som er fremgår av Prosjektbeskrivelsen. Prosjektoppgaver skal utføres i samsvar med akseptert forskningspraksis. Partneren er pålagt å overholde alle gjeldene lover og forskrifter, regler og retningslinjer som er relevante for gjennomføringen av Prosjektet, inkludert regler og retningslinjer relatert til etikk, samt anerkjente kvalitetsstandarder og normer.

Partneren er ansvarlig for å gi retningslinjer for og oppfølging av arbeidet til interne ansatte som er involverte i Prosjektet.

Innlemmelse av stipendiater må avtales mellom Partene i hvert enkelt tilfelle.

* 1. **Finansiering**

Den totale estimerte kostnaden for Prosjektet er beskrevet i Prosjektbeskrivelsen (vedlegg 1). UiO samtykker til å allokere midler til Partneren i samsvar med årsbudsjettet (vedlegg 2).

Partneren skal kreve betaling som spesifisert i fakturaopplysningene, jf. Seksjon 10. UiO skal betale alle fakturaer innen tretti – 30 – dager etter fakturadato.

1. **Prosjektbakgrunn**

Prosjektbakgrunn som er ansett som relevant ved inngåelsen av Avtalen er spesifisert i vedlegg 3.

Eierskapet til Prosjektbakgrunnen opprettholdes av parten som brakte Prosjektbakgrunnen inn i Prosjektet.

Vedlegg 3 skal holdes oppdatert fortløpende som godkjent av Partene. Eventuelle resultater fra Prosjektet som ikke inngår i Prosjektbakgrunn i henhold til vedlegg 3 og som ikke er godkjent som Prosjektbakgrunn av Partene vil automatisk bli tildelt status som Prosjektresultat.

I løpet av Prosjektperioden skal Partene ha vederlagsfri tilgang til Prosjektbakgrunnen som er nødvendig for gjennomføringen av partens eget arbeid i Prosjektet.

Partene kan forhandle om kommersiell utnyttelse av Prosjektbakgrunn som eies av den annen part. Dette skal reguleres ved skriftlig avtale.

1. **Prosjektresultater**
   1. **Eierskap**

Partene skal kommunisere skriftlig innen en – 1 – måned etter at et Prosjektresultat har blitt identifisert. Hver av Partene skal få eierskapsrettigheter til Prosjektresultatene som er produsert av parten og dennes ansatte.

I tilfeller hvor begge Partene har bidratt til utviklingen av et Prosjektresultat som ikke kan bli delt opp skal Partene ha felles eierskap til Prosjektresultatet. Partenes respektive eierandel av felles eid Prosjektresultat skal være proporsjonal med Partenes respektive finansielle og intellektuelle bidrag til utviklingen og opprettelsen av det spesifikke Prosjektresultatet. I slike tilfeller må Partene inngå en sameieavtale om felles eierskap av Prosjektresultatet. Sameieavtalen skal som et minimum inneholde en beskrivelse av det relevante Prosjektresultatet som skal eies i fellesskap og en detaljert beskrivelse av hvordan det felles eide Prosjektresultatet skal beskyttes, forsvares, styres, finansieres og brukes. Partene skal sørge for å få vern og rettigheter til Prosjektresultatene som kan ha kommersiell verdi, i den utstrekning som anses passende og nødvendig.

Partene er forpliktet til å verne om Prosjektresultater på passende måte og i nødvendig utstrekning. Dersom eierskapsrettigheter er delte mellom begge parter skal eieren av Prosjektet sørge for at korrekte og nødvendige vernetiltak blir iverksatt og gjennomført, for eierens regning. Dersom en av Partene ikke ønsker å verne om et Prosjektresultat må den aktuelle part tillate at den andre parten oppretter vern for sin egen regning.

* 1. **Bruksrettigheter**

Under hele Prosjektets varighet skal Partene ha tilgang til vederlagsfri bruk av Prosjektresultatene som er nødvendige for å gjennomføre eget arbeid i Prosjektet.

Partene skal permanent ha tilgang til vederlagsfri bruk av Prosjektresultater som skal brukes til undervisnings- og/eller forskningsformål.

Bruksrett utover det som dekkes av bestemmelsene i denne Avtalen skal skje på nærmere avtalte vilkår mellom den part som eier resultatet og den som ønsker bruksrett.

* 1. **Publisering**

Prosjektresultater skal publiseres så fort som mulig, normalt gjennom publikasjon i vitenskapelige journaler, profesjonelle møter, konferanser og lignende.

Partene skal orientere hverandre om sine planer for publisering av Prosjektresultater. Partene har en frist på fjorten – 14 – virkedager, regnet fra datoen da orienteringen ble utstedt, til å be om utsettelse av publiseringen for å kunne implementere nødvendige tiltak for å verne om Prosjektresultatene. De aktuelle forfatterne av publiseringen skal innen fjorten – 14 – virkedager forsøke å gjøre akseptable justeringer av den planlagte publiseringen, alternativt be om utsettelse på inntil tre – 3 – måneder regnet fra datoen da varsel fra parten som har produsert Prosjektresultatet ble mottatt.

Prosjektresultater vil bli publisert i felleskap i tilfellene hvor det har vært direkte samarbeid mellom Partene. I slike tilfeller vil felles forfatterskap bli basert på mengden av individuelt intellektuelt bidrag, i henhold til Vancouveranbefalingene (<http://www.icmje.org/icmje-recommendations.pdf>).

1. **Konfidensialitet**

Partene er forpliktet til å hemmeligholde all konfidensiell informasjon mottatt i eller i relasjon til Prosjektet;

* som gis skriftlig eller i en annen form og merket «konfidensielt», eller
* som ble gitt muntlig og oppgitt til å være konfidensielt, nedtegnet innen fjorten – 14 – dager, og merket konfidensielt av parten som ga informasjonen.

Konfidensiell informasjon skal ikke deles eller avsløres til andre eller publiseres, uten skriftlig samtykke fra rettighetshaveren.

Bestemmelsen gjelder ikke informasjon;

* som på tidspunktet informasjonen ble gitt var allment kjent, eller senere blir allment kjent uten at mottakeren av informasjonen er ansvarlig for dette,
* som på en lovlig måte har blitt kjent for mottaker, direkte eller indirekte gjennom andre som ikke er underlagt en tilsvarende taushetsplikt,
* som var kjent for mottakeren før informasjonen ble gitt,
* hvis bekjentgjøring kreves av myndighetene og/eller domstolene i henhold til loven,
* som er delt med Forskningsrådet i forbindelse med rapporteringskrav i henhold til kontrakten.

1. **Endringer**

Partene har rett til å fremsette et skriftlig krav om modifikasjoner eller endringer i Prosjektet så lenge disse endringene er innenfor rammeverket av Prosjektet som definert i vedlegg 1, og begge Parter samtykker. Partene skal endre årsbudsjettet tilsvarende.

1. **Ansvar**

Hver part skal selv ha ansvar for ethvert tap, skade eller personskade på partens egen, og eventuelle underleverandørers, eiendom eller personell, med mindre tapet, skaden eller personskaden har oppstått som følge av forsett eller grov uaktsomhet fra den andre parts side.

1. **Administrative kontaktpersoner**

UiO's kontaktperson: Andreas Massey

Partnerens kontaktperson: Ingrid Autran

1. **Faktureringsdetaljer**

Addresse: N/A

Merk fakturaen med: N/A

1. **Varighet og jurisdiksjon**

Avtalen trer I kraft fra og med datoen den blir signert av begge parter og vedvarer inntil prosjektperioden er over.

Avtalen kan termineres av Partene ved seks – 6 – måneders skriftlig oppsigelse. Bestemmelsene i seksjon 4, 5, 6 og 8 vil fortsatt være gjeldende mellom Partene selv etter Avtalens utløp.

Avtalen er underlagt norsk lov. Enhver tvist skal søkes løst gjennom forhandling. I tilfeller hvor forhandling ikke fører frem kan tvisten bringes inn for Oslo tingrett som riktig verneting.

1. **Signaturer**

Avtalen har blitt signert I to – 2 – originale eksemplarer. Hver av Partene beholder ett originalt eksemplar hver.

For UiO; For Partner;

Signatur: …………………………………………………… Signatur:…………………………………………………

Navn: ………………………………………………………. Navn: ………………………………………………………

Tittel …………………………………………………………. Tittel:………………………………………………………….

Dato: ………………………………………………………. Dato: …………………………………………………………

**Vedlegg 1: Prosjektbeskrivelse**

Prosjektet er et samarbeidsprosjekt mellom UiO og Østfold sykehus. Forskningsstudiet er et masterprosjekt med to studenter, Birger Bang og Andreas Massey, som er ansvarlig for datainnsamling på vegne av UiO. Ingrid Autran er legen ansvarlig for administrering av ketamin til pasientene på Østfold sykehus. Hun har også en koblingsnøkkel mellom spørreskjemaene og deltaker-ID. Attila Szabo er biokjemiker ansvarlig for analysen av spyttprøvene på UiO.

Ansvaret for databehandlingen av data innhentet under prosjektet vil være fordelt slik:

* Spyttprøver blir oppbevart midlertidig på Østfold sykehus av Andreas Massey og Birger Bang under ketamin-behandlingen i en tørris fryseboks. Deretter blir prøvene fraktet til medisinsk fakultet, UiO, hvor Attila Szabo oppbevarer prøvene i et fryserom. Disse prøvene blir analysert av Attila Szabo, kodet og oppbevart i et UiO-lagringshotell.
* Spørreskjemadataen blir innsamlet, oppbevart og transportert etter behandlingen av Andreas Massey og Birger Bang.  Skjemaene gjennomgås, kodes i avidentifisert form og lagres på et UiO-lagringshotell.
* EEG-dataen blir innsamlet og overført til sikker minnepinne av Andreas Massey og Birger Bang. Dataen blir deretter lagret på et UiO-lagringshotell.
* Symptom-endringsdataen blir registrert av Østfold sykehus. Navn erstattes med deltaker ID av Ingrid Autran. Den avidentifiserte dataen blir deretter oppbevart på et UiO-lagringshotell.

Prosjektkostnad

* UiO dekker reiseutgifter, mat til deltakere etter endt behandling, samt andre utgifter. Øvre tak per deltaker rundt 2000 kr.

Prosjektets varighet

* Prosjektet er planlagt å vare frem til 1 juli, 2023. Datainnsamling varer til 1 juli, 2023.

**Vedlegg 2: Årsbudsjett**

N/A

**Vedlegg 3: Relevant Prosjektbakgrunn tilført Prosjektet av Partene**

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

Scientific title: S*ubjective phenomenology of patients receiving ketamine-infusions as a 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 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 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 anesthetic [(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 a 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 levels [(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 anesthetics, at home in smaller doses, or using protocols minimizing such experiences).In summary, clarifying the role of the psychedelic experience induced by ketamine in the 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) has 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 outcomes [(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 anesthetics like propofol, which are highly amnesic, also show effects, 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 maximize therapeutic effect, minimize adverse effects, and 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 that increased ketamine doses 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, the 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 the 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 the treatment itself. One non-invasive method that suits this function well is electroencephalography (EEG), which is already used for similar clinical purposes such as anesthesia 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 have been associated with a 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 emphasized. For instance, if the experience is irrelevant, then clinicians should strive to reduce the uncomfortable parts by potentially administering ketamine in adjunction with other anesthetics, 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 states prior to treatment with sub-anesthetic doses of ketamine and the outcome of treatment, including the experience of treatment, and, 2) to 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 hypothesize 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 outcomes. We also hypothesize that EEG-based measures such as signal diversity and frequency band power can track the depth of psychedelic experience. Finally, we hypothesize 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 minimize 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 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 a 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 criteria 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 beside 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, the 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 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 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 categorize 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 standardized 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 a de-identified 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 analyze 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 analyzed as soon as possible after the 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 for 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 afterward. 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 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.

## References:

[Aust, S., Gärtner, M., Basso, L., Otte, C., Wingenfeld, K., Chae, W. R., Heuser-Collier, I., Regen, F., Cosma, N. C., van Hall, F., Grimm, S., & Bajbouj, M. (2019). Anxiety during ketamine infusions is associated with negative treatment responses in major depressive disorder. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *29*(4), 529–538. https://doi.org/](http://paperpile.com/b/xAKbb0/1d0L)[10.1016/j.euroneuro.2019.02.005](http://dx.doi.org/10.1016/j.euroneuro.2019.02.005)

[Ballard, E. D., & Zarate, C. A., Jr. (2020). The role of dissociation in ketamine’s antidepressant effects. *Nature Communications*, *11*(1), 6431. https://doi.org/](http://paperpile.com/b/xAKbb0/8OzZ)[10.1038/s41467-020-20190-4](http://dx.doi.org/10.1038/s41467-020-20190-4)

[Barrett, F. S., Bradstreet, M. P., Leoutsakos, J.-M. S., Johnson, M. W., & Griffiths, R. R. (2016). The Challenging Experience Questionnaire: Characterization of challenging experiences with psilocybin mushrooms. *Journal of Psychopharmacology* , *30*(12), 1279–1295. https://doi.org/](http://paperpile.com/b/xAKbb0/krx6)[10.1177/0269881116678781](http://dx.doi.org/10.1177/0269881116678781)

[Barrett, F. S., Johnson, M. W., & Griffiths, R. R. (2015). Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. *Journal of Psychopharmacology* , *29*(11), 1182–1190. https://doi.org/](http://paperpile.com/b/xAKbb0/gLYj)[10.1177/0269881115609019](http://dx.doi.org/10.1177/0269881115609019)

[Bergfeld, I. O., Mantione, M., Figee, M., Richard Schuurman, P., Lok, A., & Denys, D. (2018). Treatment-resistant depression and suicidality. In *Journal of Affective Disorders* (Vol. 235, pp. 362–367). https://doi.org/](http://paperpile.com/b/xAKbb0/VAmu)[10.1016/j.jad.2018.04.016](http://dx.doi.org/10.1016/j.jad.2018.04.016)

[Brown, F. M. (1993). Psychometric equivalence of an improved Basic Language Morningness (BALM) scale using industrial population within comparisons. *Ergonomics*, *36*(1-3), 191–197. https://doi.org/](http://paperpile.com/b/xAKbb0/q4DP)[10.1080/00140139308967872](http://dx.doi.org/10.1080/00140139308967872)

[Carhart-Harris, R. L., & Friston, K. J. (2019). REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. *Pharmacological Reviews*, *71*(3), 316–344. https://doi.org/](http://paperpile.com/b/xAKbb0/zu2p)[10.1124/pr.118.017160](http://dx.doi.org/10.1124/pr.118.017160)

[Cusin, C., Ionescu, D. F., Pavone, K. J., Akeju, O., Cassano, P., Taylor, N., Eikermann, M., Durham, K., Swee, M. B., Chang, T., Dording, C., Soskin, D., Kelley, J., Mischoulon, D., Brown, E. N., & Fava, M. (2017). Ketamine augmentation for outpatients with treatment-resistant depression: Preliminary evidence for two-step intravenous dose escalation. *The Australian and New Zealand Journal of Psychiatry*, *51*(1), 55–64. https://doi.org/](http://paperpile.com/b/xAKbb0/uD5u)[10.1177/0004867416631828](http://dx.doi.org/10.1177/0004867416631828)

[Denk, M. C., Rewerts, C., Holsboer, F., Erhardt-Lehmann, A., & Turck, C. W. (2011). Monitoring Ketamine Treatment Response in a Depressed Patient via Peripheral Mammalian Target of Rapamycin Activation. In *American Journal of Psychiatry* (Vol. 168, Issue 7, pp. 751–752). https://doi.org/](http://paperpile.com/b/xAKbb0/atFF)[10.1176/appi.ajp.2011.11010128](http://dx.doi.org/10.1176/appi.ajp.2011.11010128)

[Farnes, N., Juel, B. E., Nilsen, A. S., Romundstad, L. G., & Storm, J. F. (2020). Increased signal diversity/complexity of spontaneous EEG, but not evoked EEG responses, in ketamine-induced psychedelic state in humans. *PloS One*, *15*(11), e0242056. https://doi.org/](http://paperpile.com/b/xAKbb0/kybG)[10.1371/journal.pone.0242056](http://dx.doi.org/10.1371/journal.pone.0242056)

[Griffiths, C., Walker, K., Reid, I., da Silva, K. M., & O’Neill-Kerr, A. (2021). A qualitative study of patients’ experience of ketamine treatment for depression: The “Ketamine and me” project. *Journal of Affective Disorders Reports*, *4*, 100079. https://doi.org/](http://paperpile.com/b/xAKbb0/VqRP)[10.1016/j.jadr.2021.100079](http://dx.doi.org/10.1016/j.jadr.2021.100079)

[Haijen, E. C. H. M., Kaelen, M., Roseman, L., Timmermann, C., Kettner, H., Russ, S., Nutt, D., Daws, R. E., Hampshire, A. D. G., Lorenz, R., & Carhart-Harris, R. L. (2018). Predicting Responses to Psychedelics: A Prospective Study. *Frontiers in Pharmacology*, *9*, 897. https://doi.org/](http://paperpile.com/b/xAKbb0/IMPc)[10.3389/fphar.2018.00897](http://dx.doi.org/10.3389/fphar.2018.00897)

[Hashimoto, K. (2020). Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (R)-ketamine. *Biochemical Pharmacology*, *177*, 113935. https://doi.org/](http://paperpile.com/b/xAKbb0/Mimz)[10.1016/j.bcp.2020.113935](http://dx.doi.org/10.1016/j.bcp.2020.113935)

[Hyde, S. J. (2015). *Ketamine for Depression*. Xlibris Corporation.](http://paperpile.com/b/xAKbb0/Sq62) <https://play.google.com/store/books/details?id=HnaICgAAQBAJ>

[Jennings, P. A., Cameron, P., & Bernard, S. (2011). Ketamine as an analgesic in the pre-hospital setting: a systematic review. *Acta Anaesthesiologica Scandinavica*, *55*(6), 638–643. https://doi.org/](http://paperpile.com/b/xAKbb0/CzJb)[10.1111/j.1399-6576.2011.02446.x](http://dx.doi.org/10.1111/j.1399-6576.2011.02446.x)

[Johnston, K. M., Powell, L. C., Anderson, I. M., Szabo, S., & Cline, S. (2019). The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature. *Journal of Affective Disorders*, *242*, 195–210. https://doi.org/](http://paperpile.com/b/xAKbb0/gRbx)[10.1016/j.jad.2018.06.045](http://dx.doi.org/10.1016/j.jad.2018.06.045)

[Kadriu, B., Greenwald, M., Henter, I. D., Gilbert, J. R., Kraus, C., Park, L. T., & Zarate, C. A. (2021). Ketamine and Serotonergic Psychedelics: Common Mechanisms Underlying the Effects of Rapid-Acting Antidepressants. In *International Journal of Neuropsychopharmacology* (Vol. 24, Issue 1, pp. 8–21). https://doi.org/](http://paperpile.com/b/xAKbb0/Ygvu)[10.1093/ijnp/pyaa087](http://dx.doi.org/10.1093/ijnp/pyaa087)

[Katalinic, N., Lai, R., Somogyi, A., Mitchell, P. B., Glue, P., & Loo, C. K. (2013). Ketamine as a new treatment for depression: a review of its efficacy and adverse effects. *The Australian and New Zealand Journal of Psychiatry*, *47*(8), 710–727. https://doi.org/](http://paperpile.com/b/xAKbb0/rz2B)[10.1177/0004867413486842](http://dx.doi.org/10.1177/0004867413486842)

[Khalili-Mahani, N., Martini, C. H., Olofsen, E., Dahan, A., & Niesters, M. (2015). Effect of subanaesthetic ketamine on plasma and saliva cortisol secretion. *British Journal of Anaesthesia*, *115*(1), 68–75. https://doi.org/](http://paperpile.com/b/xAKbb0/hqBj)[10.1093/bja/aev135](http://dx.doi.org/10.1093/bja/aev135)

[Krystal, J. H., Abdallah, C. G., Sanacora, G., Charney, D. S., & Duman, R. S. (2019). Ketamine: A Paradigm Shift for Depression Research and Treatment. In *Neuron* (Vol. 101, Issue 5, pp. 774–778). https://doi.org/](http://paperpile.com/b/xAKbb0/XTJ3)[10.1016/j.neuron.2019.02.005](http://dx.doi.org/10.1016/j.neuron.2019.02.005)

[Lai, R., Katalinic, N., Glue, P., Somogyi, A. A., Mitchell, P. B., Leyden, J., Harper, S., & Loo, C. K. (2014). Pilot dose-response trial of i.v. ketamine in treatment-resistant depression. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *15*(7), 579–584. https://doi.org/](http://paperpile.com/b/xAKbb0/CHBt)[10.3109/15622975.2014.922697](http://dx.doi.org/10.3109/15622975.2014.922697)

[Li, L., & Vlisides, P. E. (2016). Ketamine: 50 Years of Modulating the Mind. *Frontiers in Human Neuroscience*, *10*, 612. https://doi.org/](http://paperpile.com/b/xAKbb0/oF1L)[10.3389/fnhum.2016.00612](http://dx.doi.org/10.3389/fnhum.2016.00612)

[Little, A. (2009, July 15). *Treatment-Resistant Depression*.](http://paperpile.com/b/xAKbb0/5SYF) <https://www.aafp.org/afp/2009/0715/p167.html>

[Loo, C. K., Gálvez, V., O’Keefe, E., Mitchell, P. B., Hadzi-Pavlovic, D., Leyden, J., Harper, S., Somogyi, A. A., Lai, R., Weickert, C. S., & Glue, P. (2016). Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatrica Scandinavica*, *134*(1), 48–56. https://doi.org/](http://paperpile.com/b/xAKbb0/Pp90)[10.1111/acps.12572](http://dx.doi.org/10.1111/acps.12572)

[Markopoulou, K., Papadopoulos, A., Juruena, M. F., Poon, L., Pariante, C. M., & Cleare, A. J. (2009). The ratio of cortisol/DHEA in treatment resistant depression. *Psychoneuroendocrinology*, *34*(1), 19–26. https://doi.org/](http://paperpile.com/b/xAKbb0/zJPe)[10.1016/j.psyneuen.2008.08.004](http://dx.doi.org/10.1016/j.psyneuen.2008.08.004)

[Mashour, G. A., Ben Abdallah, A., Pryor, K. O., El-Gabalawy, R., Vlisides, P. E., Jacobsohn, E., Lenze, E., Maybrier, H. R., Veselis, R. A., Avidan, M. S., & PODCAST Research Group. (2018). Intraoperative ketamine for prevention of depressive symptoms after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *British Journal of Anaesthesia*, *121*(5), 1075–1083. https://doi.org/](http://paperpile.com/b/xAKbb0/35j1)[10.1016/j.bja.2018.03.030](http://dx.doi.org/10.1016/j.bja.2018.03.030)

[Matveychuk, D., Thomas, R. K., Swainson, J., Khullar, A., MacKay, M.-A., Baker, G. B., & Dursun, S. M. (2020). Ketamine as an antidepressant: overview of its mechanisms of action and potential predictive biomarkers. *Therapeutic Advances in Psychopharmacology*, *10*, 2045125320916657. https://doi.org/](http://paperpile.com/b/xAKbb0/OUhr)[10.1177/2045125320916657](http://dx.doi.org/10.1177/2045125320916657)

[Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry: The Journal of Mental Science*, *134*, 382–389. https://doi.org/](http://paperpile.com/b/xAKbb0/bTKV)[10.1192/bjp.134.4.382](http://dx.doi.org/10.1192/bjp.134.4.382)

[Muttoni, S., Ardissino, M., & John, C. (2019). Classical psychedelics for the treatment of depression and anxiety: A systematic review. *Journal of Affective Disorders*, *258*, 11–24. https://doi.org/](http://paperpile.com/b/xAKbb0/1Y7B)[10.1016/j.jad.2019.07.076](http://dx.doi.org/10.1016/j.jad.2019.07.076)

[Nour, M. M., Evans, L., Nutt, D., & Carhart-Harris, R. L. (2016). Ego-dissolution and psychedelics: Validation of the ego-Dissolution Inventory (EDI). *Frontiers in Human Neuroscience*, *10*, 269. https://doi.org/](http://paperpile.com/b/xAKbb0/w66B)[10.3389/fnhum.2016.00269](http://dx.doi.org/10.3389/fnhum.2016.00269)

[Paslakis, G., Gilles, M., Meyer-Lindenberg, A., & Deuschle, M. (2010). Oral administration of the NMDA receptor antagonist S-ketamine as add-on therapy of depression: a case series. *Pharmacopsychiatry*, *43*(1), 33–35. https://doi.org/](http://paperpile.com/b/xAKbb0/kHSY)[10.1055/s-0029-1237375](http://dx.doi.org/10.1055/s-0029-1237375)

[Paul, R., Schaaff, N., Padberg, F., Möller, H.-J., & Frodl, T. (2009). Comparison of racemic ketamine and S-ketamine in treatment-resistant major depression: report of two cases. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *10*(3), 241–244. https://doi.org/](http://paperpile.com/b/xAKbb0/hA5B)[10.1080/15622970701714370](http://dx.doi.org/10.1080/15622970701714370)

[Peill, J. M., Trinci, K. E., Kettner, H., Mertens, L. J., Roseman, L., Timmermann, C., Rosas, F. E., Lyons, T., & Carhart-Harris, R. L. (2022). Validation of the Psychological Insight Scale: A new scale to assess psychological insight following a psychedelic experience. *Journal of Psychopharmacology* , *36*(1), 31–45. https://doi.org/](http://paperpile.com/b/xAKbb0/MxuH)[10.1177/02698811211066709](http://dx.doi.org/10.1177/02698811211066709)

[Roseman, L., Haijen, E., Idialu-Ikato, K., Kaelen, M., Watts, R., & Carhart-Harris, R. (2019). Emotional breakthrough and psychedelics: Validation of the Emotional Breakthrough Inventory. *Journal of Psychopharmacology* , *33*(9), 1076–1087. https://doi.org/](http://paperpile.com/b/xAKbb0/lTPA)[10.1177/0269881119855974](http://dx.doi.org/10.1177/0269881119855974)

[Schartner, M. M., Pigorini, A., Gibbs, S. A., Arnulfo, G., Sarasso, S., Barnett, L., Nobili, L., Massimini, M., Seth, A. K., & Barrett, A. B. (2017). Global and local complexity of intracranial EEG decreases during NREM sleep. *Neuroscience of Consciousness*, *2017*(1), niw022. https://doi.org/](http://paperpile.com/b/xAKbb0/u2zg)[10.1093/nc/niw022](http://dx.doi.org/10.1093/nc/niw022)

[Segmiller, F., Rüther, T., Linhardt, A., Padberg, F., Berger, M., Pogarell, O., Möller, H.-J., Kohler, C., & Schüle, C. (2013). Repeated S-ketamine infusions in therapy resistant depression: a case series. *Journal of Clinical Pharmacology*, *53*(9), 996–998. https://doi.org/](http://paperpile.com/b/xAKbb0/qFrn)[10.1002/jcph.122](http://dx.doi.org/10.1002/jcph.122)

[Sumner, R. L., Chacko, E., McMillan, R., Spriggs, M. J., Anderson, C., Chen, J., French, A., Jung, S., Rajan, A., Malpas, G., Hay, J., Ponton, R., Muthukumaraswamy, S. D., & Sundram, F. (2021). A qualitative and quantitative account of patient’s experiences of ketamine and its antidepressant properties. *Journal of Psychopharmacology* , *35*(8), 946–961. https://doi.org/](http://paperpile.com/b/xAKbb0/n8VP)[10.1177/0269881121998321](http://dx.doi.org/10.1177/0269881121998321)

[Vlisides, P. E., Bel-Bahar, T., Nelson, A., Chilton, K., Smith, E., Janke, E., Tarnal, V., Picton, P., Harris, R. E., & Mashour, G. A. (2018). Subanaesthetic ketamine and altered states of consciousness in humans. *British Journal of Anaesthesia*, *121*(1), 249–259. https://doi.org/](http://paperpile.com/b/xAKbb0/nTez)[10.1016/j.bja.2018.03.011](http://dx.doi.org/10.1016/j.bja.2018.03.011)

[Yaden, D. B., & Griffiths, R. R. (2021). The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. *ACS Pharmacology & Translational Science*, *4*(2), 568–572. https://doi.org/](http://paperpile.com/b/xAKbb0/VQ2K)[10.1021/acsptsci.0c00194](http://dx.doi.org/10.1021/acsptsci.0c00194)

[Zhan, Y., Zhou, Y., Zheng, W., Liu, W., Wang, C., Lan, X., Deng, X., Xu, Y., Zhang, B., & Ning, Y. (2020). Alterations of multiple peripheral inflammatory cytokine levels after repeated ketamine infusions in major depressive disorder. *Translational Psychiatry*, *10*(1), 246. https://doi.org/](http://paperpile.com/b/xAKbb0/V1Oi)[10.1038/s41398-020-00933-z](http://dx.doi.org/10.1038/s41398-020-00933-z)

[Zsido, A. N., Teleki, S. A., Csokasi, K., Rozsa, S., & Bandi, S. A. (2020). Development of the short version of the spielberger state-trait anxiety inventory. *Psychiatry Research*, *291*, 113223. https://doi.org/](http://paperpile.com/b/xAKbb0/U692)[10.1016/j.psychres.2020.113223](http://dx.doi.org/10.1016/j.psychres.2020.113223)