Bringing computational psychiatry to clinical practice: Patient stratification for successful administration of intranasal s-ketamine in treatment-resistant depression

Published: 08-01-2024
Last updated: 06-05-2024

Primary objective:(1) Assess baseline (i.e., before treatment) differences between esketamine-responders and non-responders on key elements of value-based decision making (including reward- and punishment sensitivity, approach-avoidance tendencies,...

Ethical review	Approved WMO
Status	Pending
Health condition type	Mood disorders and disturbances NEC
Study type	Observational invasive

Summary

ID

NL-OMON56574

Source
ToetsingOnline

Brief title
ComPass-TRD

Condition

- Mood disorders and disturbances NEC

Synonym
hard to treat depression; treatment resistant depression

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,ZonMW

Intervention

Keyword: depression, esketamine, habenula, prediction

Outcome measures

Primary outcome

Primary endpoint is the change (relative to baseline) in clinician-rated MADRS score (Montgomery 1979) at 4 weeks.

On a neural level changes in blood oxygen level dependent (BOLD) signal is the main study parameter, especially within the habenula and circuitry involved in value-based decision-making.

On a behavioural level, action-context specific Pavlovian-instrumental-transfer effects are the main study parameters.

Secondary outcome

Changes in resting state functional connectivity as a function of treatment (response)

Changes in structural brain characteristics (cortical thickness, subcortical volumes) as a function of treatment (response)

Study description

Background summary

Depression is one of the most prevalent (globally ~5% of adults) psychiatric disorders due to its incidence and chronicity rates. It is a leading cause of disability world-wide and contributes greatly to the global burden of disease. Although different psychological and pharmacological treatments are available, about 25% of depressed patients remain clinically symptomatic, even after several conventional treatment steps, making treatment resistant depression (TRD) an extremely debilitating and costly condition. Finding the right treatment is often a long and painful search of trial and error. We are thus in direct need of more efficacious and efficient treatment regimens. Understanding why some people do respond to a certain treatment and why others don*t, is a key step in the roadmap towards more efficacious and efficient treatment regimens.
Moreover, understanding a depressive condition as a corollary of disturbed neural circuitry related to relatively well-understood value-based decision making, gives us a stepping-stone for advancing our knowledge on the mode of action of effective treatments, which in turn will enable us to address variability in treatment effects.
Esketamine was the first new treatment in decades to be approved for the treatment of TRD in 2021. This treatment has an estimated response rate of ~50% after four weeks in TRD patients, which makes this treatment an asset for this patient group and leaves much room for improvement. Esketamine has an innovative, yet still marginally understood, mode of action in terms of neurotransmission (primarily via down-stream effects of NMDA-receptors instead of monoaminergic reuptake inhibition) and time scale (in terms of hours compared to weeks) compared to conventional antidepressants. There is thus a need to better understand the mode of action of esketamine and its relation to variability in treatment effects.
Thus, in the current proposal we will assess how basic learning task performance, probing value-based decision making, and associated neural activity in regions which are also likely to be involved in the effect of esketamine, differ between patients with TRD who respond to esketamine and those who do not respond to esketamine.
To do this we will invite TRD patients to two neuroimaging sessions respectively before and after 4 weeks of their treatment. This latter point is chosen as this is the point in clinical practice when the first choice of treatment prolongation is taken (thus, when the first differentiation between responders and non-responders is made).

Study objective

Primary objective:
(1) Assess baseline (i.e., before treatment) differences between esketamine-responders and non-responders on key elements of value-based decision making (including reward- and punishment sensitivity, approach-avoidance tendencies, motivation and effort-investments) and related neural pathways (including the activation/connectivity of the habenula, raphe nucleus, ventral tegmental area, (ventral) striatum, anterior cingulate cortex,

insula, ventromedial prefrontal cortex and hippocampus/amygdala).

Secondary objectives:
(2) Establish difference in neurobehavioral changes between responders and non-responders from pre-to-post treatment.
(3) Contribute to neurobiological validation of clinical change by relating clinical change to change in key nodes of habenula-related monoaminergic pathways from pre-to-post treatment.
(4) Contribute neurobiological validation of clinical predictors/risk factors by relating these to key nodes of habenula-related monoaminergic pathways.

Study design

Observational, prospective, longitudinal cohort study.

Study burden and risks

Participants will have to attend two meetings at the MRI labs for neurocognitive measurements and will also have to answer multiple questionnaires as part of clinical assessments (see study design). The neurocognitive measurements include feedback on performance that might be frustrating or uncomfortable (e.g., shock).
All other procedures that the patients will undergo, are clinical routine and would have been carried out regardless whether patients would participate in our study.
Considering the extensive exclusion criteria, the screening procedure, and constant monitoring of the subjects we do not expect (S)AE side effects for MRI measurements. MRI measurements themselves do not pose any risk if appropriate precautions are made. However, the noise and the relative confined space of the MRI scanner may cause discomfort to some subjects.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

To be eligible to participate in this study, a subject must meet all of the following criteria:
- Clinical diagnosis of primary MDD, preferably confirmed by a structured clinical interview (MINI/SCID-I)
- Treatment Resistant Depression, defined as non-response to at least two antidepressants used at adequate dosages for a minimum of 6 weeks
- Age >18 years old (no maximum age)
- Current use of an antidepressant

Exclusion criteria

Een potentiële proefpersoon die aan een van de volgende criteria voldoet, wordt uitgesloten van deelname aan deze studie:

Kan niet spreken, lezen en/of begrijpen van het Nederlands (VMBO-niveau)

Voorgeschiedenis van significante neurologische aandoeningen

Zwangerschap

Mentaal niet bekwaam om toestemming te geven voor informed consent

Standaard contra-indicatie voor MRI:
o Onveilige metalen of apparaten in het lichaam (cardiale pacemaker, cochleair implantaat, aneurysmaklem)
o Eerdere hersenoperatie

o Matige tot ernstige claustrofobie

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2023
Enrollment:	52
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	08-01-2024
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL85391.091.23