Predicting and Understanding Neurocognitive Mechanisms of Relapse Prevention: a randomized controlled trial of preventive cognitive therapy in remitted Major Depressive Disorder using fMRI and pupillometry

Published: 02-09-2015
Last updated: 15-05-2024

The primary aim of this study is to understand the neurocognitive mechanisms by which preventive cognitive therapy obtains its preventive effects in remitted depressed patients. Using functional MRI in combination with pupillometry and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON47768

Source
ToetsingOnline

Brief title
NEW PRIDE

Condition

- Mood disorders and disturbances NEC

Synonym
depresssion, major depressive disorder

Research involving

Human

Sponsors and support

Primary sponsor: Cognitive Neuroscience Center
Source(s) of monetary or material Support: NWO-VENI grant 016.156.077,Hersenstichting Fellowship F2014(1)-21

Intervention

Keyword: depression, fMRI, prevention, relapse

Outcome measures

Primary outcome

Primary outcome measures are the preventive cognitive therapy-induced changes in attentional biases, prefrontal control, and the pupil dilation response, measured with cognitive paradigms, functional MRI and pupillometry, respectively.

Secondary outcome

Secondary outcome measures include changes in mood, affect, (depressive) cognitions and long term course of the depressive disorder (relapse: yes/no at 18-month follow-up).

Study description

Background summary

Major Depressive Disorder (MDD) is the most prevalent psychiatric disorder affecting approximately 25% of the population at least once in their lives. 40% of patients will experience relapse into another, life-disrupting episode within two years after recovery, which significantly contributes to the personal and economic burden of MDD. As risk for relapse and chronic-MDD increases dramatically with the number of previous episodes, preventing relapse early in the disease-course is a major clinical goal. Yet, mechanisms facilitating relapse are poorly understood, thereby hampering selection and

development of appropriate preventive treatments for individual patients.

Preventive cognitive therapy (CT) was proven effective in lowering relapse-risk, superior to the predominantly prescribed maintenance-treatment with antidepressant medication. Surprisingly, the working mechanisms of this successful preventive therapy have never been studied. However, understanding the neurocognitive mechanisms of preventive-CT in remitted-MDD will help us to understand relapse and relapse-prevention.Unfortunately, preventive-CT is not effective for all patients in lowering the relapse-risk and currently it is unclear for clinicians who will benefit from preventive-CT and who will not. Here we propose that studying the mechanisms of preventive-therapy will provide a unique opportunity to develop markers that predict individual preventive-treatment success.

In this study we will investigate the neurocognitive mechanisms that explain the preventive effects of preventive cognitive therapy and we will additionally investigate which neurocognitive measures can predict successful preventive treatment. We hereby focus on core-abnormalities characterizing abnormal information processing in depression: 1) abnormal attention to negative information, leading to a selective, negative perception of the world; and 2) inadequate regulation of mood states, reflected in an increased tendency to engage in, and difficulty to disengage from negative mood states. Problems in regulating attention and emotional information have been related to inadequate top-down control exerted by the brain*s lateral- and medial-prefrontal cortex (PFC) over limbic regions associated with primary emotion processing, such as the amygdala, striatum, and insula. Previously we showed that functional and structural abnormalities of the lateral- and medial-PFC, including the pregenual-anterior-cingulate cortex (pgACC), persist in the remitted phase and even predict an unfavourable course. Therefore these regions must be considered critical to understand and predict relapse and preventive-treatment response and may constitute key targets for lowering the relapse-risk. We hypothesize that targeting the persisting frontal abnormalities is crucial and most effective to prevent relapse and that preventive-CT is potent in doing that.

Although functional imaging may provide essential information on relapse-risk and treatment-efficacy, it is not feasible to refer each remitted patient to costly fMRI scanning. Therefore, we propose to translate neurocognitive mechanisms for use in clinical practice by using the autonomic pupil dilation response (PDR) as reflection of PFC-control over limbic areas, essential for adequate emotion regulation. The PDR is an index of emotional arousal and cognitive effort associated with sympathetic nervous system activity. It was shown to predict emotion regulation success and activation of prefrontal and limbic brain-regions associated with effortful emotion regulation in symptomatic MDD-patients and controls . Moreover, it was shown to accurately predict CT-response in symptomatic-MDD. Yet, its validity for predicting regulation- and treatment-success in the remitted phase has not been established.

We will innovatively validate the PDR as an index of brain-responsivity during effortful emotion regulation and bias-processing in remitted-MDD before and after preventive-CT. Translating neuroimaging research for applications in clinical practice denotes a major step forward in preventing relapse for individual patients.

We hypothesize that:
- remitted depressed patients will show lower prefrontal control during the active regulation of emotional states compared to never-depressed individuals;
- preventive-CT in remitted-MDD obtains its preventive effect by boosting control function of the lateral- and medial-PFC, thereby dampening the activation of limbic regions for negative information. This will lower preferential processing of negative information. At the same time, increased PFC-control may increase preferential processing of positive information, additionally lowering the likelihood of a prevailing negative mood.
- Furthermore, we hypothesize that pre-treatment lateral-PFC activation and connectivity of the lateral-PFC with the medial-PFC and amygdala during negative emotion processing predicts favourable treatment response.
- prefrontal control during emotion regulation will be reflected in pupil dilation responsivity in remitted depressed patients and increased prefrontal control following treatment is associated with an increase in pupil dilation during emotion regulation.

Study objective

The primary aim of this study is to understand the neurocognitive mechanisms by which preventive cognitive therapy obtains its preventive effects in remitted depressed patients. Using functional MRI in combination with pupillometry and neuropsychological assessments, we will test whether preventive cognitive therapy in remitted patients results in increased prefrontal control, and whether this increased prefrontal control results in a decrease in attentional biases and an increase in emotion regulation capacity.

Secondary, this study aims to:
- predict individual preventive treatment success in remitted depressed patients based on neurocognitive measures;
- translate neurocognitive principles to clinically useful measures to predict and monitor individual preventive cognitive therapy success.

Study design

The proposed study is a randomized controlled trial to study preventive cognitive therapy in remitted MDD-patients. In the experimental condition, eight sessions of preventive cognitive therapy will be prescribed and in the control condition, no treatment is prescribed. The study is characterized by an open design where patients and the principal investigator is informed on the

treatment condition. However, the test administrators will be blinded to the treatment condition, in order to prevent biases in scoring the tests.

The study consists of 4 phases:
The first phase concerns the baseline measurement, including questionnaires (2 hours), neuropsychological testing (1 hour) and an functional MRI-session (1 hour). During the neuropsychological and MRI-measurement, pupil behavior will be additionally assessed. The questionnaires and interview are administered in order to objectify rest-abnormalities in affect, cognitions and attentional deployment.functional MRI is administered to assess prefrontal control and primary emotional reactivity of subcortical brain structures. At baseline a healthy control group will be included for cross-sectional comparisons to establish residual abnormalities in the remitted MDD group in neuropsychological and neurophysiological measures.

In the second phase, patients will be treated with eight sessions of protocolized preventive cognitive therapy by experienced and qualified psychotherapists. Patients randomized to the control condition will not receive any treatment.

The third phase concerns the follow-up measurement, in which all measurements from the baseline measurement will be repeated. An interview to objectify recurrence of depressive pathology according to DSM-IV criteria will also be administered. This assessment takes place three months following the baseline measurement.

In the fourth phase, all participants will be invited to assess the clinical course over the past 18 months. For this purpose the SCID-I interview will be administered in addition to a self-rated questionnaire to objectify severity of depressive symptomatology (Inventory of Depressive Symptomatology). The purpose of this 18-months follow-up measurement is to inventory which patients relapsed into a new depressive episode following treatment and which patients are still remitted. This allows us to define neurocognitive predictors of relapse and to study how treatment-induced changes in frontal control contributed to long term course in remitted patients. This assessments takes place 18-months after the baseline measurement.

Intervention

The experimental group will receive eight sessions of protocolized preventive therapy, delivered in individual sessions by experienced and licensed psychotherapists. The patients in the waiting list control group will not receive any treatment in the interval between the baseline measurement and the three-month follow-up measurement. Nevertheless, after the three-month follow-up measurement, these patients will be offered preventive cognitive therapy.

Study burden and risks

During the first and third phase (baseline and 3-month follow-up measurement, respectively) patients and controls are requested to fill out questionnaires about their personal situation and emotional experiences. No advantages of such standardized inventarisation are known or to be expected. This clinical assessment part will take about 120 minutes to complete.
Next participants will be exposed to a 3 T magnetic field for approximately 60 minutes. No side effects have been described so far. On rare occasions a peripheral nerve (abdomen) is stimulated by the changing magnetic gradients, this will cause an itchy feeling, but is not harmful. On the same day, participants perform several cognitive tests, which will take up a maximum of 60 minutes. During the fMRI session and the cognitive testing, participants are presented with pictures depicting scenes of various emotional connotation. Pictures can be experienced as very negative and very positive. During these sessions, we will keep track of the affective fluctuations of the participants. Also, at the end of each measurement, an exit interview will be held in which the purpose of the experiments is explained and in which specific attention is paid to any possible long lasting effects of the exposure to the negative emotional scenes.

In total, the phase 1 (baseline measurement) will take up 5 hours (including breaks), phase 2 (treatment) approx. 6 hours, phase 3 (three-month follow-up) 5,5 hours (including breaks), and phase 4 (diagnostic interview to assess course) will take up a maximum of one hour. In total, participation to the study will take 19,5 hours for patients in the treatment condition, 13,5 hours for patients in the waiting-list control condition, and 7 hours for the healthy control participants, incl. screening (2 hrs_. The study phases are preceded by a screening phase to determine eligibility for participating in the study. This takes approx. 2 hours.

Contacts

Public
Selecteer

Ant. Deusinglaan 2
Groningen 9713 AW
NL
Scientific
Selecteer

Ant. Deusinglaan 2
Groningen 9713 AW

NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients and healthy controls:
- between 18 en 60 years of age, Patients:
- MDD diagnosis lifetime according to DSM criteria as assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)
- current remission (>2 months; according to criteria defined in DSM IV))
- >2 major depressive episodes in past 5 years
- recency of last episode: <2 years
- currently not using any anti-depressant medication (>4 weeks)

Exclusion criteria

Patients:
- current major depressive episode
- current use of antidepressant medication, Patients and healthy controls:
- neurological problems (incl. epilepsy, dementia, neuromuscular illness)
- drug abuse, alcohol dependency, or at this moment a psychiatric disorder found out during the screening
- use of psychotropic medication other than infrequent use of benzodiazepine (not in 48 hours prior to research, < 3 times per week)
- any other current DSM-IV Axis-I diagnosis, as objectified with the SCID-I
- MR-contraindications:
*any risk of having metal particles in the eye
*(suspected) pregnancy
*claustrophobia
* implants incompatible with the MRI-scanner (such as pacemaker, heart

valves, vascular clips, eye-implants, copper containing intra-uterine devices, or non-removable piercings, ear prosthesis or other metal implants in the body)
*the refusal to be informed of structural brain abnormalities that could be detected during the fMRI experiment
- the refusal to sign the informed consent
- history of contusion cerebri with >15 minutes loss of consciousness
- visual impairments other than correctable by glasses or lenses

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-04-2016
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	02-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-02-2016
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-12-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 26793
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL53205.042.15
Other	voorlopig NTR-nr: 22764
OMON	NL-OMON26793