Early-life stress, the endocannabinoid system, and fear memory extinction

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23960

Source
Nationaal Trial Register

Brief title
ELTCAN

Health condition

posttraumatic stress disorder

Sponsors and support

Primary sponsor: Radboudumc
Source(s) of monetary or material Support: Radboudumc
Chinese Scholarship Counsil

Intervention

Outcome measures

Primary outcome

autonomic nervous system measurement (skin conductance, heart rate, and pupil dilation responses) and subjective scores on 5-point scale to rate the expectancy of the appearance of the unconditioned stimuli (USs) to fear-conditioned stimuli one day after extinction (i.e., safety learning).

Secondary outcome

Neuroimaging data (founctional and structural neuro images), chemical data (in saliva, and in blood),self-report questionnaires

Study description

Background summary

Rationale: Early life stress (ELS) constitutes a major risk factor for the development and persistence of mental disorders, increasing rates of posttraumatic stress disorder (PTSD). A first-line and empirically validated approach to treat this disorder is Prolonged Exposure Therapy (PE), one component of which involves repeated exposure to fear-linked cues to produce ¡¥¡¥extinction¡¦¡¦ of fear and to prevent avoidance responses to these cues. However, a significant number of patients have incomplete responses or fail to sustain improvements over time, mainly due to the fact that extinction learning, which is the core mechanism underlying exposure-based therapy, is vulnerable to the return of pathological fear. A promising novel strategy is adding drug treatment to exposure therapy in a timed manner to improve the long-term outcome of exposure therapy. Recent findings indicate that hydrocortisone, a synthetic form of the endogenous stress hormone cortisol, may improve stress adaptation and enhance the extinction of fear memories. Critically, recent data from rodent models demonstrate that glucocorticoids exert their actions via recruitment of the endogenous cannabinoid (endocannabinoid) system. Pre-clinical studies moreover suggest that ELS causes disturbances in the endocannabinoid system which might render hydrocortisone ineffective as adjuvant treatment to exposure therapy. A striking and recurrent clinical observation is that a large percentage of PTSD patients, in particular those with a chronic course associated with ELS, uses cannabis as ¡§self-medication¡¨ to alleviate their symptoms. Also, initial results from studies in healthy volunteers show that exogenous cannabinoids may strengthen extinction learning.
We will therefore compare the efficacy of £G9-tetrahydrocannabinol (THC; dronabinol), one of the active components of natural cannabis, and hydrocortisone in enhancing extinction learning in healthy volunteers with and without ELS.

Objective: We hypothesize that in healthy individuals with ELS, THC, which directly targets the endocannabinoid system, is more effective than hydrocortisone in improving stress adaptation and extinction learning in an experimental model of exposure therapy compared to healthy individuals without ELS.

Study design: 2*3 mixed factorial double-blind, placebo-controlled, cross-over interventional study with Drug (THC, hydrocortisone or placebo) as within-subject factor and Group (ELS vs. Non-ELS) as between-subject factor.

Study population: Two groups of healthy individuals (n=25 each) with either a history of ELS or without a history of ELS.

Intervention: To investigate the role of the endocannabinoid system in fear memory extinction and stress adaption, we will use established behavioral and neuroimaging paradigms. We will test the different effectiveness of two different pharmacological interventions: THC (7.5mg), hydrocortisone (20mg) in fear memory recall test. The control condition will use a double placebo procedure.

Study objective

We hypothesize that in healthy individuals with Early-life stress (ELS), THC, which directly targets the endocannabinoid system, is more effective than hydrocortisone in improving stress adaptation and extinction learning in an experimental model of exposure therapy compared to healthy individuals without ELS.

Study design

One day after drug administration

Intervention

To investigate the role of the endocannabinoid system in fear memory extinction and stress adaption, we will use established behavioral and neuroimaging paradigms including (1) a classical fear conditioning, extinction and recall task, (2) an autobiographical memory recall task and (3) dynamic facial expression task. We will test the different effectiveness of two different pharmacological interventions: THC (7.5mg), hydrocortisone (20mg) in fear memory recall test. The control condition will use a double placebo procedure.

Contacts

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Eligibility criteria

Inclusion criteria

For both groups:

„Ï Healthy volunteers between 18 and 45 years of age.

„Ï Predominant right-handedness.

„Ï History of taking cannabis.

For ELS group:

„Ï Comply the inclusion standard with questionnaires: ¡§Maltreatment and Abuse Chronology of Exposure Scale (MACE-X)¡¨. There are 10 subscales in MACE-X, the criterion for each subscale is listed here, all types of exposure of trauma should be before ten years old. There are six subscales which are very relevant to severe childhood maltreatment: Emotional Neglect, Parental Nonverbal Emotional Abuse, Parental Physical Maltreatment, Parental Verbal Abuse, Sexual Abuse, or Witnessing Interparental Violence. Participant should reach at least one criterion of those six subscales to be included for certain types of childhood maltreatment:

„X In emotional neglect subscale, (the cut-off is 2 items out of 5).

„X In non-verbal emotional abuse subscale, (the cut-off is 4 out of 6).

„X In parental physical maltreatment subscale, (the cut-off is 4 items).

„X In parental verbal abuse subscale, (the cut-off is 3 items out of 4).

„X In sexual abuse subscale, (the cut-off is 2 items out of 7).

„X In witnessing interparental violence subscale, (the cut-off is 2 items out of 5).

There are four subscales which are less relevant to severe childhood maltreatment, the criterion of each subscale are listed here below, if participants only fulfil the criteria of any one or more of those four subscales, they will not be included in ELS group:

„X In peer emotional abuse subscale, (the cut-off is 4 items out of 5).

„X In peer physical bullying subscale, (the cut-off is 2 items out of 5).

„X In physical neglect, (the cut-off is 2 items out of 5).

„X In witnessing violence to siblings subscale, (the cut-off is 1 items out of 4).

For Non-ELS group: Since we need to recruit participants in control group with no experiences of early-life stress, thus we will include people who score 0 on six very relevant to severe childhood maltreatment (SCM) subscales and also below threshold of other four less relevant to severe childhood maltreatment (LSCM) subscales in ¡§Maltreatment and Abuse Chronology of Exposure Scale (MACE-X)¡¨.

Exclusion criteria

For both groups:

„Ï Body mass index lower than 18.5 or higher than 30.

„Ï Abnormal hearing or (uncorrected) vision.

„Ï Average use of psychotropic medication or recreational drugs weekly or more.

„Ï Habitual smoking, i.e. more than a package of cigarettes per week and a self-reported inability or unease to cease smoking for 24 hours prior to testing.

„Ï Use of psychotropic medication, or of recreational drugs over a period of one week prior to each test session, and use of alcohol within the last 24 hours before each measurement.

„Ï Regular use of corticosteroids.

„Ï History of psychiatric treatment or current psychiatric treatment. (e.g., severe mood disorders, mania, anorexia nervosa, schizophrenia or borderline personality disorder)

„Ï History of neurological treatment or current neurological treatment.

„Ï History of endocrine treatment or current endocrine treatment. (e.g., pheochromocytoma, hyperthyroidism, Cushing¡¦s syndrome)

„Ï History of repeated (more than once) of autonomic failure (e.g., vasovagal reflex syncope).

„Ï Contraindications for MRI scanning (e.g., pacemaker, implanted metal parts, deep brain stimulation, claustrophobia)

„Ï Use of medication that may interact with THC or hydrocortisone, for THC, taking Rifampicin, Ketoconazole, and Omeprazole at this moment; For Hydrocortisone, taking taking mifepristone at this moment.

„Ï Cognitive impairment (MMSE < 26)

„Ï Pregnancy

„Ï Night shift work

Study design

Design

Study type:	Interventional
Intervention model:	Factorial
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2018
Enrollment:	48
Type:	Anticipated

Ethics review

Not applicable

Application type:	Not applicable

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
NTR-new	NL6687
NTR-old	NTR6857
Other	NL62274.091.17 : ELTCAN1

Study results