Memory formation under stress in humans - the importance of the Mineralocorticoid Receptor

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cognitive and attention disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON35544

Source
ToetsingOnline

Brief title
Memory & the MR

Condition

- Cognitive and attention disorders and disturbances

Synonym
memory and anxiety disorders, stress disorders

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: NWO Grant "Memory formation under stress: The emerging importance of the brain mineralocorticoid receptor" provided to Prof.

Dr. Guillén Fernández (Nijmegen);Prof. Dr. Melly Oitzl (Leiden-Amsterdam) and Prof. Dr. Marian Joëls (Utrecht;Amsterdam)

Intervention

Keyword: cortisol, fear, fMRI, mineralocorticoid receptor

Outcome measures

Primary outcome

At the behavioural level, the main study parameter in the spatial memory task is accuracy (i.e. how well subjects remember the right location for a given object learned earlier) and the strategy used (i.e., automatic stimulus response association or elaborate spatial map strategy). For fear acquisition we assess how fast and accurate subjects learn the relationship between specific stimuli and threat using skin conductance responses. At the brain system level, we seek to investigate whether neural response patterns obtained by fMRI can reveal the neural mechanism by which MR activation is causing stress induced changes in spatial memory and fear learning.

Secondary outcome

- Baseline levels of salivary cortisol (the first 3 saliva samples are used to compute an individual baseline cortisol level per participant)

- Changes in blood pressure and heart rate

- Changes in resting state connectivity due to stress and administration of an MR blocker

- Personality and life events questionnaires:These questionnaires partly ask for very private details (such as abuse in early childhood) but are important as stress, early life experiences and personality traits have substantial

impacts on endocrine measures, brain development and cognitive performance in adulthood. Thus we aim to use the following questionnaires:

• State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

• Life Threatening Events (LTE) (Brugha & Cragg, 1990).

• Shortened Temperament and Character Inventory (TCI; Cloninger, 1994).

• Trier Inventory of Chronic Stress (Trier Inventory of Chronic Stress, TICS-LE. Unpublished English Version).

• Herinneringen aan de opvoeding, short form (EMBU-s; Arrindell et al., 1999), a questionnaire on early life parental care.

- Mood state questionnaires:

• Positive Affect Negative Affect (PANAS) (Watson et al., 1988).

• State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) to assess state anxiety.

• Mood rating scale (Bond & Lader, 1974), extended with 8 items to assess evaluation of the study situation.

Study description

Background summary

Stress and stress hormones (e.g. glucocorticoids, GCs) have profound impact on memory, an effect of fundamental importance for psychological trauma formation. Specifically, stress causes a switch towards a more automatic in contrast to elaborate processing as shown in spatial memory tasks. This switch appears dependent on one type of GCs receptors, the mineralocorticoid receptor (MR) as assessed in rodents. Stress also impacts on the acquisition of fear memory. It has been suggested that fear acquisition is also dependent on MR. To explore this role of MRs for the first time in humans, we will combine sophisticated

behavioral tasks in a functional magnetic resonance imaging (fMRI) setting with a well-established stress-induction procedure and a pharmacological manipulation of the MR. This series of human experiments is complemented by parallel experiments in rodents and slice preparation conducted by collaborators in Leiden and Utrecht.

Study objective

The main objective is to investigate the role of MRs in memory acquisition and recall during stress and non-stress conditions. Specifically, we are interested in two domains of memory, spatial and fear memory. Secondary objectives are to determine brain regions involved in memory changes under stress and the influence of Spironolacton on these stress-induced changes in neural activation patterns during memory formation and recall.

Study design

We plan a double-blind, placebo-controlled, between-subject study using a full-factorial design with the factors being stress (stress vs. control), and MR activation (Spironolacton vs. placebo). We will probe the effects of 400mg Spironolacton on memory formation under stress and non-stress conditions. Thus, four groups of subjects will be tested: Stress & Spironolacton, Stress & Placebo, Control & Spironolacton, Control & Placebo. The study will take place in the afternoon on two consecutive days for a given subject.

Intervention

Half of the subjects will undergo a slightly modified version of the Socially Evaluated Cold Pressure Task (SECPT; Schwabe, Haddad, & Schachinger, 2008) to induce stress. The other half will undergo a control condition meant to cause no stress. Furthermore, half the subjects of the stress- and the non stress-group will receive a single dose Spironolacton (400mg tablet) 90 minutes before undergoing fMRI; the other participants will receive placebo.

Study burden and risks

Considering the application of a classical, widely used drug, strict exclusion criteria, the screening procedure, continuous monitoring of the subjects and the experiences of colleagues in Amsterdam and Hamburg with applicating Spironolacton in young, healthy subjects, we do not expect SAE or any other side effects. For more information we refer to the Summary of Product Characteristics (SPC) of Spironolacton.
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.
The stress induction procedure will most likely cause distress in the

participants. This can hardly be avoided in a study investigating the mechanisms underlying the effects of stress on human memory. To minimize discomfort as much as possible, we will use a safe, often applied and very short stress-induction procedure (3 minutes) compared to other paradigms frequently used.
Further discomfort might be caused by procedures such as providing a blood sample for screening, filling out questionnaires about adverse early-life experiences or chronic stress, and the time spend on the study. Furthermore, in order to evoke a fear response, participants will be subjected to mild electric stimuli (e.g. "shocks"). This procedure has been widely used in humans in classical aversive conditioning paradigms, also in our previous studies (CMO protocol number 2010/257). The strength of the electric stimuli is set individually for each subject using a staircase procedure so that the actual stimulation is uncomfortable but not painful. The 'common knowledge' sensation most closely mimicking the sensation of the electric stimuli is hitting one*s funny bone (medial epicondyle of the humerus). These settings are necessary to be able to study fear learning.

The consent discussion starts sufficiently in advance of the initiation of study-related procedures to allow potential subjects time to reflect on the potential benefits and risks and possible discomforts. Participants are informed about the study when they are screened (usually days before inclusion) and the risk associated with participation in this study in total can be regarded as minimal. The results of this study will provide us with better insight into the mechanisms underlying memory changes under stress. This might in turn help for better under-standing of how traumatic memories are built and finally provide deeper insight into phenomena like posttraumatic stress disorder which pose an enormous burden on individuals, their families and the society at large.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male, healthy volunteers
- Age 18 - 35 years
- Normal or corrected-to-normal vision
- Normal uncorrected hearing
- Body mass index between 18.5 and 30
- Willingness and ability to give written informed consent and willingness and ability to understand the nature and content, to participate and to comply with the study requirements

Exclusion criteria

- Anuria,
- Acute or history of renal insufficiency / impairment of renal excretory function (or creatinine levels > 1.1 mg/dl at screening)
- Hyperkalemia (or potassium levels of > 5.0 mEq/L at screening)
- History of psychiatric treatment /current psychiatric treatment
- History of neurological treatment /current neurological treatment
- History of endocrine treatment /current endocrine treatment
- History of autonomic failure (e.g., vasovagal reflex syncope)
- History of psychotropic medication (e.g. antidepressants)
- History of hepatic impairments
- History of cardiovascular diseases
- Hypotension (< 90 / 60 mmHG)
- Bradycardia / Tachycardia (heart rate < 50 or > 100 at rest)
- Use of any medication on a regular basis
- Metal objects in or around the body
- Irregular sleep/wake rhythm (e.g., regular nightshifts or cross timeline travel)
- Claustrophobia

- Use of recreational drugs weekly or more often
- Smoking of more than 5 cigarettes per day
- Average use of more than 3 alcoholic beverages daily and self-reported inability or un-ease to cease drinking alcohol for 24 hours prior to testing.
- Caffeine consumption 3 hours before testing
- Professional sports or participation in competitions (as Spironolacton can lead to a positive doping test)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-02-2012
Enrollment:	96
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aldactone
Generic name:	Spironolactone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	30-09-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-12-2011
Application type:	First submission
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

ID: 19893
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2011-003493-85-NL
CCMO	NL37819.091.11
OMON	NL-OMON19893