Neural mechanisms of noradrenaline and cortisol effects on memory accuracy vs. generalization over time

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Ethical review	Approved WMO
Status	Completed
Health condition type	Anxiety disorders and symptoms
Study type	Interventional

Summary

ID

NL-OMON52476

Source
ToetsingOnline

Brief title
Noradrenaline and cortisol effects on memory consolidation

Condition

- Anxiety disorders and symptoms

Synonym
posttraumatic stress disorder

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: DFG (Deutsche Forschungsgemeinschaft)

Intervention

Keyword: cortisol, memory, neuroimaging, noradrenaline

Outcome measures

Primary outcome

The main study parameters are measures of the autonomic nervous system (skin conductance response).

Secondary outcome

Secundary study parameters are pupil dilation meausres, subjective (expectancy ratings) indices of fear learning and recall and extinction, item memory performance and neuronal activity and connectivity patterns (hippocampus, amygdala, neocortex).

Study description

Background summary

During a stressful experience, noradrenaline and cortisol interact to induce strong and lasting memories. However, the role of these stress mediators in modifying the quality of these memories is still unclear. According to the memory transformation hypothesis, memories become less accurate over time as they are being transformed from contextually detailed, hippocampus-dependent memories to more gist-like, neocortical representations. Rodent studies suggests that noradrenaline and cortisol differentially modulate this memory transformation process. Whereas noradrenaline was shown to maintain long-term memory accuracy and hippocampus dependency, cortisol contributed to early memory generalisation, suggesting that stressful memories become independent from the hippocampus more rapidly. We developed a new paradigm to investigate memory quality in humans and hypothesize that increases in noradrenaline during learning maintain long-term memory accuracy and hippocampus dependency, whereas enhanced cortisol levels promote memory generalization and a more rapid transformation of the memory trace to neocortical structures.

Study objective

The aim of this experiment is to determine the differential effects of noradrenaline and cortisol on memory accuracy versus generalization and to investigate the divergent effects of these stress mediators on the neural mechanisms underlying the reorganisation of detailed into gist-like memories over time.

Study design

This experiment is a double-blind placebo controlled between subject intervention study.

Intervention

The study includes 4 different groups: 40mg atomoxetine + placebo, 20mg hydrocortisone + placebo, 40mg atomoxetine + 20mg hydrocortisone, 2 placebo tablets. Within each group, both tablets are taken once at the beginning of the experiment (atomoxetine ~120min before the MRI task, hydrocortisone ~60min before the MRI task).

Study burden and risks

We estimate the burden and risks of this study as negligible.
Subjects participate in two experimental sessions which are 28 days apart. Both sessions consist of questionnaires, cognitive tasks and physiological measurements (skin conductivity, pupil dilation, heart rate, respiration). All tasks and the structural and resting state scans take place inside a 3T MRI scanner (2 scan sessions à 1.5h). Loud noise in the scanner and lying in a small confined space may lead to discomfort in some participants. During session 1, participants receive an oral administration of atomoxetine, hydrocortisone or both or placebo. Both atomoxetine and hydrocortisone do not have a potential for abuse, they have a relatively short half-life and rapid clearance which minimizes accumulation of the drugs, and they have no known interaction effects. Therefore, these drugs have a very favourable safety profile and a high tolerability. Only a single and relatively low dose of the drugs is administered similar to other experimental studies that use atomoxetine and hydrocortisone as challenge agents (none of which reported any adverse events or side effects). During both sessions, participants perform a virtual environment task, which has been optimized to prevent navigation-induced motion sickness. During session 1, participants perform a differential fear conditioning task that is embedded in the virtual environment. In this task, participants sometimes receive mild electric shocks to evoke a fear response. This procedure has been widely used in humans in classical aversive conditioning paradigms.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Healthy volunteers between 18 and 35 years
Right-handed
Normal uncorrected hearing
Normal or corrected-to-normal vision

Exclusion criteria

Current regular medication intake (including corticosteroids and adrenergic medication, monoamine oxidase inhibitors, CYP2D6 inhibitors such as SSRIs)
Pregnancy
Contraindications for MRI scanning (e.g. pacemaker, implanted metal, claustrophobia)

Current or history of any psychiatric disorder
Disorders of the autonomic system
Cardiovascular or cerebrovascular conditions
Hepatic insufficiency
Renal insufficiency
Glaucoma
Current or history of pheochromocytoma
Recreational drug-use
Smoking
Body mass index lower than 18 or higher than 30

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:	Completed
Start date (anticipated):	10-05-2022
Enrollment:	112
Type:	Actual

Ethics review

Approved WMO

Date:	22-02-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	03-05-2022
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	NL73831.091.20