Sex differences in the acute effects of guanfacine on activation of the brain stress system in individuals with an alcohol use disorder

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON51610

Source
ToetsingOnline

Brief title
SANE-study (Sex-differences, alcohol misuse and Negative Emotions)

Condition

- Other condition

Synonym
Alcohol use disorder; alcohol addiction

Health condition

psychische stoornissen, alcoholverslaving

Research involving

Human

Sponsors and support

Primary sponsor: Vrije Universiteit
Source(s) of monetary or material Support: Brain and Behavior Research Foundation 70.000 USA dollar

Intervention

Keyword: alcohol use disorder, guanfacine, pharmacological MRI, Sex differences

Outcome measures

Primary outcome

The primary outcome of this study is neural activation of the amygdala and changes in amygdala-PFC connectivity in response to negative emotional picture (compared to neutral pictures).

Secondary outcome

Secondary outcomes are i) neural activation of the amygdala and changes in amygdala-PFC connectivity in response to alcohol-related cues (compared to neutral cues), ii) alcohol and emotional cue-induced subjective responses (craving and arousal) iii) resting heart-rate variability and iv) glutamate concentrations in the dorsal anterior cingulate cortex (dACC) and v) resting state connectivity

Study description

Background summary

Alcohol use disorder (AUD) is a leading risk factor for global disease burden. Unfortunately, AUD treatment is only moderately successful. While the prevalence of AUD is 2-3 times higher among men than women, this gap is quickly closing. Nonetheless, women are structurally ignored in AUD research, impeding

the development of much-needed sex-tailored interventions. It has been suggested that alcohol use and relapse in women is more strongly driven by stress-related factors than in men with an AUD. More specifically, these sex differences in stress-related alcohol use are thought to be mediated by the noradrenergic mechanisms in the prefrontal cortex.

Study objective

The objective of this study is to investigate the role of noradrenergic functioning in sex-specific dysregulation of the brain stress system in individuals with an AUD. This will be done by investigating sex differences in the acute effect of a α2a- noradrenergic receptor agonist (guanfacine) on activation of the brain stress system in individuals with AUD, using task-based pharmacological Magnetic Resonance Imaging (phMRI). It is hypothesized that following a placebo, women compared to men with an AUD will show stronger emotional cue-induced activation of the amygdala, and lower amygdala-PFC connectivity. Guanfacine is expected to reduce emotional cue-induced activation and strengthen cue-induced amygdala-PFC connectivity in women with an AUD more so than it does in men.

Study design

Randomized, single blind, placebo controlled, cross-over phMRI study

Study burden and risks

Participants will need to come to the Spinoza Center twice, for a duration of 5 hours. These sessions will consist of an informed consent procedure (first session only), the oral administration of guanfacine/placebo, continuous measurement of heart-rate variability using an ambulatory monitoring system (VU-AMS), the assessment of clinical and demographic information using an online questionnaire (maximum duration of 60 minutes) and the actual phMRI scan (45 minutes). During the time between the last questionnaire and start of the phMRI study (approximately 3 hours), there will be no study procedures (except for the continuous monitoring of HRV). In sum, participants will spend 2x 5 hours in the AMC (of which approximately 3 hours concern actual research time, and the remaining hours consist of waiting time, needed for guanfacine to achieve optimal blood plasma levels. The emotional cue-reactivity task that will be used during the phMRI scan, makes use of standardized pictures from the IAPS data set, which has been frequently used in research in both clinical and non-clinical populations. No adverse side effects of this fMRI paradigm are expected. Guanfacine has been used as a pharmacological challenge in various studies, without adverse side effects, and is approved for the treatment of children and adolescents with ADHD. Guanfacine can have an acute cardiovascular effect (lowering heartrate), but especially the extended-release guanfacine is associated with a relatively low side-effect profile. Hence the burden

associated with guanfacine administration is expected to be low. While the participants themselves will not have direct beneficial effects of the study, the knowledge resulting from this study has the potential to pave the way for the development of sex-specific, pharmacological treatment options for alcohol use disorder. The overall nature and extent of the added risk associated with participation in the current study is to be classified as negligible and the burden can be considered minimal.

Contacts

Public
Vrije Universiteit

van der boechorstraat 7
Amsterdam 1081 BT
NL
Scientific
Vrije Universiteit

van der boechorstraat 7
Amsterdam 1081 BT
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Meeting at least 2 of the 11-DSM5 criteria for alcohol use disorder
- age 25-45

Exclusion criteria

- MRI contraindications
- having a cardiovascular disease
- the presence of cardiovascular risk factors (a history of sudden fainting without reason, a relative that died as a consequence of heart failure before the age of 60, a relative with pacemaker)
- heartrate < 60, systolic blood pressure < 120 on the day of testing
- the use of psychotropic medication (e.g., Ritalin, SSRI's, medication acting on cardiovascular system; The use of CYP3A4-inductors and inhibitors)
- a history of neurological disorders
- for women: being pregnant, or breastfeeding
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- An indication of a substance use disorder other than alcohol use disorder based on the drug use disorder identification test (exclusion when score is higher than 11)
- smoking more than 10 cigarettes per day
- a positive alcohol breath test on the day of testing

BMI < 18 or > 30

Study design

Design

Study type:	Observational invasive
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	03-01-2022
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO Date:	21-01-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL79897.018.21