The impact of norepinephrine on top-down and bottom-up neural processing

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1) To investigate the effect of atomoxetine on resting-state fMRI measures of network functional connectivity.2) To assess the effect of atomoxetine on several task performance variables, that are hypothesized to reflect tonic LC-NE activity.3) To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON40584

Source
ToetsingOnline

Brief title
Norepinephrine and neural processing

Condition

- Other condition

Synonym
healthy

Health condition

wetenschappelijk onderzoek met gezonde vrijwilligers

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: European Research Council (ERC)

Intervention

Keyword: bottom-up processing, fMRI, norepinephrine, top-down processing

Outcome measures

Primary outcome

~Drug intervention~

In one session, subjects will receive 40 mg of the selective norepinephrine reuptake inhibitor atomoxetine (Navarra, et al., 2008), orally administered. Although other recent studies have used dosages of 80 mg (Graf, et al., 2011), here we opt for the typical starting dose used in clinical practice, 40 mg, to avoid the reported side effects of increased heart rate at high atomoxetine doses (Heil, et al., 2002). In the other session, either one week earlier or one week later, subjects will receive a placebo pill.

~MRI data acquisition~

Functional neuroimaging will be performed at the 3T fMRI scanner of the LIBC, located in the the LUMC. One resting-state fMRI scan series will last approximately 7 minutes. For registration purposes, one T1-weighted scan will be acquired for each subject. During RS-fMRI acquisition, the cardiac and respiratory signal will be acquired using a flexible pressure belt and a pulse oximeter. In addition, pupil diameter will be concurrently measured using an EyeLink 1000 fMRI-compatible eye tracker.

~Saliva samples~

We will collect saliva using Salivette sampling devices in order to measure corticol levels and the secretion of salivary alpha-amylase, a valid biomarker for central noradrenergic activity and NE release (reviewed in Segal & Cahill, 2009). Saliva will be collected three times per session: At baseline (right before the treatment); after completing the MRI scans; and after subjects complete all tasks. Saliva samples will be stored at -20 °C after completion of the session until biochemical analysis takes place.

~Questionnaires~

The State-Trait Anxiety Inventory for Adults (Spielberger, Goruch, Lushene, Vagg & Jacobs, 1983) is a standard anxiety questionnaire that measures trait anxiety. Two reviews have identified a relationship between anxiety and NE activity (Tanaka, Yoshida, Emoto & Ishii, 2000; Howells, Stein & Russell, 2012). Tanaka and colleagues reviewed anxiety and stress manipulations in the animal literature that increased NE release from the LC, and psychopharmacological manipulations of NE levels that altered the anxiety response. Howells and company reviewed studies of human subjects with anxiety disorders, and animal models of anxiety disorders, highlighting abnormal LC structure and LC dysfunction in these subjects. Howells and company in particular noted the relationship between trait anxiety and baseline NE activity. Thus, trait anxiety could be an important regressor in our statistical models.

~Random dot motion (RDM) task~

Participants will perform a speeded response time version of the random dot motion (RDM) paradigm. The RDM is a popular task that has been widely employed to investigate the neural basis of human perceptual decision making. During task performance, participants are instructed to maintain fixation on a centrally presented cross and decide as quickly and accurately as possible whether the dominant direction of motion of a small cloud of moving dots is leftward or rightward. During a given trial of the task, a proportion of the dots move in the same direction from one moment to the next, whereas the remaining dots move randomly within the cloud. Hence, participants must make their direction discrimination decisions in the presence of sensory noise. Participants will begin each session (atomoxetine or placebo) by practicing the RDM task at an easy level of discrimination in order to become comfortable with the task. Subsequent to this, they will complete a task block consisting of trials of variable difficulty. This block will allow us to calibrate the appropriate difficulty level for each participant and session, and control for non-specific effects of testing session on task performance. After ingestion of atomoxetine or placebo, participants will complete two task blocks at the difficulty level determined by the previous testing phase. We will characterize the effects of the drug manipulation on decision making by fitting a drift-diffusion model to the behavioral data. Our prediction is that atomoxetine will increase the parameter value indicating the degree of trial-to-trial variability in the rate of evidence accumulation.

~Go/nogo task~

Subjects will perform a go/nogo task. On each trial, the stimulus can be a go stimulus (green circle: respond as quickly as possible) or a nogo stimulus (red square: withhold overt response). In half of the blocks, there will be 20% nogo trials (i.e. typical go/nogo design). Chamberlain et al. (2006, 2009) have found that in this type of design, atomoxetine improves nogo performance, which they attributed to an effect of atomoxetine on response inhibition. However, Yu and Dayan*s (2005) account suggests that atomoxetine will lead subjects to overestimate the frequency of unexpected nogo stimuli (i.e. the degree of unexpected uncertainty) and therefore facilitate withholding of responses. To dissociate the two accounts, in the other half of the blocks there will be 80% nogo trials (i.e. typical oddball design). The response inhibition account predicts improved nogo performance (fewer false alarms) under atomoxetine. Yu and Dayan predict that atomoxetine will lead subjects to overestimate the frequency of go trials, which will lead to impaired performance on nogo trials (more false alarms). This task will last approximately 30 mins. During this task we will collect EEG data from 3 scalp electrodes (Fz, Cz, Pz) to examine the effect of atomoxetine on the P3.

~Statistical analysis~

No previous studies have examined the effect of atomoxetine on resting-state fMRI connectivity analyses. Therefore, no formal calculation was performed. However, a previous pharmacological resting-state fMRI study of Khalili-Mahani et al. (2012), conducted in the LUMC, found robust effects of morphine and

alcohol with 12 subjects. Previous studies that found effects of atomoxetine on response inhibition in a task similar to the go/nogo task, used ~20 subjects (e.g., Chamberlain et al., 2009). Therefore, we assume sufficient power by including 24 subjects in the proposed research.

For fMRI measurements, the relative contribution of each subject will be compared between the atomoxetine and the placebo condition, using mixed-model analysis of variance for repeated measures. This approach permits detecting differerences in resting-state brain activity between drug and placebo across the pre- and post-drug measurements.

Secondary outcome

n.v.t.

Study description

Background summary

The locus coeruleus (LC) is the brainstem neuromodulatory nucleus responsible for most of the norepinephrine (NE) released in the brain. The LC-mediated brain-wide noradrenergic innervation increases the responsivity of efferent target neurons (Berridge & Waterhouse, 2003), potentiating any neural activity present concurrent with LC activation (Servan-Schreiber, Printz, & Cohen, 1990). Although cell recordings in non-human primates have yielded a wealth of information regarding the dynamics of the noradrenergic system, to date there has been little empirical research on the activation dynamics and function of this system in humans. This requires the development of indirect measures, or the measurement of changes in behavior and brain activity brought about by pharmacological manipulations of the noradrenergic system. We propose a psychopharmacological study that uses resting-state fMRI and behavioral methods to test two models of the effect of tonic NE levels on neurocognitive processing (Yu & Dayan, 2005; Aston-Jones & Cohen, 2005).

~Tonic activity of the LC-NE system~

Besides phasic increases in activity following motivationally significant stimuli, the LC-NE system shows tonic changes in (baseline) LC activity (i.e. changes happening over the course of multiple seconds or minutes). It has long been known that tonic changes in LC activity instigate changes in arousal, from sleep (minimal LC activity) to alertness (intermediate) to high arousal and anxiety (high). However, only recently have researchers begun to examine the cognitive functions of these LC-mediated changes in arousal. This has led to the two influential models discussed below.

~Adaptive gain theory: tonic NE increases decision noise~
According to the adaptive gain theory (Aston-Jones & Cohen, 2005), different modes of LC activity serve to regulate a fundamental tradeoff between exploitation and exploration. The LC phasic mode is characterized by intermediate tonic LC activity and selective phasic LC bursts to motivationally significant stimuli, thus promoting exploitative behavior (i.e. pursuing known sources of reward). In contrast, the LC tonic mode is characterized by elevated tonic LC activity and the absence of selective phasic responses. This nonselective increase in NE release produces an enduring and nondiscriminative increase in neural responsivity. This uniform increase in responsivity is tantamount to increasing network noise and favors explorative behaviors.
One of the goals of the proposed research is to test the hypothesis that an increase in tonic NE levels is indeed associated with increased noise, or variability, in decision making. To this end we will increase NE levels pharmacologically with the noradrenergic reuptake inhibitor atomoxetine (e.g. Bari & Aston-Jones, 2012), and characterize the effects of this manipulation on decision making in a random-dot motion task, by fitting a drift-diffusion model to the behavioral data. Our prediction is that atomoxetine will increase the parameter value indicating the degree of trial-to-trial variability in the rate of evidence accumulation.

~Yu & Dayan (2005): tonic NE levels regulate the balance between top-down and bottom-up neural processing~
Yu and Dayan (2005) proposed that tonic LC activity increases due to unexpected uncertainty arising from unanticipated changes in a task context, resulting in strong violations of top-down expectations. According to Yu and Dayan, the elevated tonic NE release in turn promotes bottom-up relative to top-down neural processing, which facilitates learning about the changes in the external environment, and thus allows updating of top-down expectations. This account is closely related to the adaptive gain theory*s assumption that the tonic LC mode promotes exploration. To support their model, Yu and Dayan cited animal work suggesting that NE selectively suppresses intracortical and feedback synaptic transmission, while sparing, or even boosting, thalamocortical processing (e.g., Kobayashi et al., 2000). To test this claim in humans, we will examine how functional connectivity patterns in the brain change when NE is increased. To this end we will examine the effect of atomoxetine on network connectivity, as measured with resting-state fMRI (Lu & Stein, 2013). In addition, we will concurrently record pupil diameter, which has been proposed to closely track LC

activity (Aston-Jones & Cohen, 2005). This will allow us to relate within-session fluctuations in functional connectivity to fluctuations in this hypothesized correlate of LC activity.
Yu and Dayan predicted that a pharmacological increase in tonic NE should lead to overestimation of the degree of unexpected uncertainty, and should therefore accelerate the detection of unexpected changes in task contingencies. This could explain why animals show improvements in attentional-set shifting when tonic NE levels are increased. In the proposed research we will test the prediction in humans by examining the effect of atomoxetine on performance in response to unexpected target stimuli (oddball paradigm) and unexpected nontarget stimuli (nogo paradigm). Yu and Dayan*s account suggests that atomoxetine will lead subjects to overestimate the frequency of these unexpected stimuli (i.e. the degree of unexpected uncertainty) and therefore facilitate subjects* reactions to these stimuli.
During this task we will collect EEG data, to examine the effect of atomoxetine on the P3 (or P300) component of the event-related potential, an ERP correlate of phasic NE release (Nieuwenhuis et al., 2005).

Study objective

1) To investigate the effect of atomoxetine on resting-state fMRI measures of network functional connectivity.
2) To assess the effect of atomoxetine on several task performance variables, that are hypothesized to reflect tonic LC-NE activity.
3) To examine the effect of atomoxetine on an ERP correlate of phasic NE release (P3)

Study design

~Design~
The proposed study will use a double-blind, placebo-controlled, cross-over design.

~General procedure~
The proposed study will consist of two sessions of fMRI and behavioral data collection: an atomoxetine session and a placebo session. The study will start in the EEG/challenge lab on the ninth floor of the LUMC (Psychiatry), and move down to the fMRI room on the first floor about half an hour after the subject arrives. The subject will return to the EEG room after being scanned twice (pre- and post-drug), separated by a long interval. There are 75 minutes of tasks to perform in the EEG/challenge lab, before and after the fMRI scans. Altogether, each session will last approximately four hours. Subjects will be administered the drug 85 minutes before the first post-drug measurement (resting-state fMRI), to ensure that post-drug measurements are collected during peak blood levels (Chamberlain, Muller, Blackwell, Robbins, et al., 2006; Graf, et al., 2011). Data collection will be completed 135 minutes after

taking the drug, well within the window of time when the drug should still be having an effect on cognition (Sauer, Ring, & Witcher, 2005).

~Session time line~

-65 min. Arrival (5 min.)
-60 min. Practice RDM task + baseline measurement (25 min.)
-35 min. Transfer to fMRI room / change into MRI clothes (10 min.)
-25 min. MRI: T1 and resting state (25 min.)
0 min. Atomoxetine/placebo, administered orally (5 min.)
5 min. State-Trait Anxiety Inventory (10 min.)
15 min. Practice go/nogo task (10 min.)
25 min. Relax (60 min)
75 min. Implicit grammar task 2:50 post-drug (10 min.)
85 min. MRI: resting state (15 min.)
100 min. Change into normal clothes / transfer to 9th floor (10 min.)
110 min. RDM task (20 min.)
130 min. Short break (5 min.)
135 min. Go/nogo task (30 min.)
165 min. Debriefing (5 min.)
170 min. End of experiment
235 min. total duration

Intervention

In one session, subjects will receive 40 mg of the selective norepinephrine reuptake inhibitor atomoxetine (Navarra, et al., 2008), orally administered. Although other recent studies have used dosages of 80 mg (Graf, et al., 2011), here we opt for the typical starting dose used in clinical practice, 40 mg, to avoid the reported side effects of increased heart rate at high atomoxetine doses (Heil, et al., 2002). In the other session, either one week earlier or one week later, subjects will receive a placebo pill.

Study burden and risks

Side effects of atomoxetine
A single dose of atomoxetine has not been reported to have long-lasting effects, either adverse or beneficial. Short-term
side effects of the drug can include fatigue, increased heart rate, akathisia and dry mouth, which have been shown to
disappear around 2 hours after drug ingestion (Chamberlain, Muller, Blackwell, Clark, et al., 2006; Chamberlain, Muller,
Blackwell, Robbins, et al., 2006). For some groups, atomoxetine does carry more serious effects: individuals with
glaucoma, with heart disease, or taking monoamine oxidase inhibitors (MAO inhibitors). These groups will be excluded from

participation.

fMRI
There are no known risks associated with participating in an fMRI study. This is a noninvasive technique involving no catheterizations or introduction of exogenous tracers. Numerous human subjects have undergone magnetic resonance studies without apparent harmful consequences. Radiofrequency power levels and gradient switching times used in these studies are within the FDA approved ranges. Some people become claustrophobic while inside the magnet and in these cases the study will be terminated immediately at the subject's request.

Pupillometry
The eye-tracker system uses detailed analysis of high-definition video to record pupil diameter at any given time during the experiment. The subjects do not have to wear any special apparatus for the eye-tracker to work, and are at no significant risk of any type of injury or discomfort due to this aspect of the experiment.

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

Healthy adult subjects with no history of neurological disorder/disease and no counter-indications to 3 Tesla MRI or to atomoxetine, and no personal relationship with the researchers will be included in this study. All participants will be right-handed native Dutch speakers with normal vision or contact lenses.

Exclusion criteria

Potential participants will be prescreened for contra-indications for 3 Tesla fMRI and atomoxetine, which include metal implants, heart arrhythmia, claustrophobia, glaucoma, hypertension and use of anti-depressants or psychotropic medication and possible pregnancy (in adult females). They will additionally be prescreened for head trauma, premature birth, learning disabilities, and history of neurological or psychiatric illness. Finally, left-handed individuals will be excluded from the study because some left-handers have substantially different brain organization relative to right-handers.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-03-2014

Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	26-02-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL47476.058.13