The Impact of Norepinephrine on the Fidelity of Neural Representations

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The primary objective of this study is to measure the effect of a psychopharmacological manipulation of NE on fMRI measures of the fidelity of cortical representation.The secondary objective is to determine if increased levels of cortical...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON38650

Source
ToetsingOnline

Brief title
Norepinephrine and neural representation

Condition

- Other condition

Synonym
healthy

Health condition

scientific investigation of healthy subjects

Research involving
Human

Sponsors and support

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

Intervention

Keyword: decision making, fMRI, neural representation, norepinephrine, perception

Outcome measures

Primary outcome

fMRI and Pupilometry Data acquisition

Functional neuroimaging will be performed at the 3T fMRI scanner located in the Radiology department of the LUMC. BOLD activity will be measured using standard gradient-echo echoplanar imaging (EPI) parameters. Simultaneously, pupil diameter will be measured using an EyeLink 1000 fMRI compatible eye tracker.

Saliva Samples

We will collect saliva using Salivette sampling devices in order to measure 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 four times in total: At baseline (2 minute before taking atomoxetine); after completing the affirmation of beliefs questionnaire (95 minutes after taking atomoxetine); after coming out of the scanner (156 minutes after drug administration); and after subjects complete all tasks (210 minutes after drug administration). 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 which measures trait anxiety, a correlate of baseline NE activity (Tanaka, Yoshida, Emoto & Ishii, 2000).

The affirmation of beliefs questionnaire is a brief questionnaire previously shown to be sensitive to violations of expectation (e.g. Proulx & Heine, 2008), which in turn is thought to be a factor that influences NE release (e.g. Yu & Dayan, 2005). The subject will read a set of short descriptions of non-violent crimes (e.g. damaging a parked car in a small collision and leaving the scene without taking responsibility), and minor heroic acts (e.g. returning found wallet). There will be ten descriptions in total (five crimes and five heroic acts) and the subject will be asked to select the monetary value for the ticket (in the case of the crime) or reward (in the case of a heroic act) in each case, from a range indicated on the questionnaire. Each description should take less than a minute to read, and the subject will be asked to complete the questionnaire within 15 minutes.

Statistical analysis

Standard analysis methods in FSL (www.fmrib.ox.ac.uk/fsl) and custom routines in MATLAB will be used to analyze the MRI data. For the multivariate pattern analysis we will use a Gaussian naïve Bayes classifier to discriminate between categories on the basis of the spatial pattern of neural activity. Through an

iterative dimensionality reduction process we will train the classifier to distinguish between categories, and identify which voxels are most helpful for that task. Once we have identified an appropriate set of voxels, we will represent the pattern of activity across those voxels on each trial as a vector (extending from the zero-point along all dimensions, to the coordinate of the relative activity pattern in multi-dimensional space), yielding a set of vectors for each category. We will quantify fidelity as the mean angular deviation between vectors within a category, whereby smaller deviation indicates greater fidelity. This method has been used previously by our collaborators (Schurger et al., 2010).

Secondary outcome

not applicable.

Study description

Background summary

The locus coeruleus (LC) is the brainstem neuromodulatory nucleus responsible for most of the norepinephrine (NE) released in the brain. It has widespread projections throughout the neocortex. When an animal is actively engaged in performing a task, LC neurons exhibit a rapid, phasic increase in discharge rate to task-relevant and otherwise motivationally salient stimuli. The ensuing release of NE in cortical areas temporarily increases the responsivity (or gain) of these areas to their afferent input (Berridge & Waterhouse, 2003), selectively potentiating any activity present concurrent with LC activation. Some researchers have suggested that this transient, LC-induced increase in responsivity serves to optimize simple decision making (i.e., selecting a response based on perceptual evidence) by increasing the signal-to-noise ratio (SNR) of signal processing in the cortex (e.g. Usher, Cohen, Servan-Schreiber, Rajkowski & Aston-Jones, 1999; Aston-Jones & Cohen, 2005). However, other researchers have suggested that increases in NE levels serve to facilitate a network reset that allows a complete reorganization of neural activity to facilitate a new set of responses (e.g. Bouret & Sara, 2005; Yu & Dayan 2005;

Dayan & Yu, 2006). Still others have focused on the role of NE in long-term potentiation (e.g. Harley, 2007). To date there has been scarce research directly investigating the impact of NE on human cognition. We propose a psychopharmacological study that uses cutting edge fMRI analysis techniques to directly test if NE increases the SNR of cortical processing. In addition, to fully take advantage of the long duration of our psychopharmacological manipulation, we will have subjects perform a few additional tasks aimed at testing other proposed effects of NE.

1.1 Norepinephrine and Signal-to-Noise Ratio

Norepinephrine enhances the responsivity of neurons to both excitatory and inhibitory inputs, effectively increasing the gain of the neuron (Serban-Schreiber, Prinz, & Cohen, 1990). Serban-Schreiber and colleagues demonstrated that when a homogenous increase in gain is applied to all composite neurons in a neural network, the SNR of the network is improved, such that signals are enhanced and noise is decreased. In target detection tasks, this means there are fewer misses (strong signals) and fewer false alarms (less noise). It follows from this that if the neural network is representing information, it should represent that information with greater precision, or fidelity. That is, there should be less variability (noise) in the way the network represents the same information from trial to trial than when the SNR is lower. A new technique of analyzing fMRI data, called multivariate pattern analysis (MVPA) offers a direct way of testing this hypothesis.

1.2 MVPA and Representational Space

MVPA is a method of extracting more information from fMRI data than traditional analyses, by taking into account the relative activity of voxels in an area of interest (e.g. Mur, Bandettini, and Kriegeskorte, 2009; Pereira, Mitchell, and Botvinick, 2009). By plotting the relative activation in each voxel of interest relative to others, a neural network state can be represented as a single point in multidimensional space (this representational space will have as many dimensions as there are voxels in the analysis). In this multi-dimensional, representational space, network states provoked by the same category of event will tend to cluster together, whereas network states elicited by different categories will tend to be distal from one another. Haxby and colleagues (2001) used this powerful technique to reliably discriminate between the brain activity elicited by eight categories of visual stimuli: houses, faces, cats, chairs, scissors, shoes, jugs, and nonsense pictures. That is, they could reliably predict from the brain activity which category of stimulus the participants viewed on any given trial. As an even greater demonstration of the information that can be obtained with MVPA, Haynes and colleagues (2007) were able to reliably distinguish between trials where subjects chose to add two numbers together, versus trials where the subject chose to subtract one number from the other. These examples of classification involved determining which category a trial belonged to by determining which category cluster the network state was closest to: Distance in multi-dimensional space is a direct measure of the similarity between representations.

1.3 The Fidelity of Neural Representations

Schurger, Pereira, Treisman, and Cohen (2010) used distance in representational space as a measure of the fidelity of a neural representation. Instead of examining the separation between clusters of network states, they examined separation within clusters. A cluster of network states can be diffuse and spaced out widely, or it can be tight and compact. A tightly spaced cluster indicates that the neural representation varied very little across multiple trials of the same category, rather like the tightly spaced arrows of an expert archer. This measure of the fidelity of the neural representation (they used the term reproducibility) was the measure that significantly differed between consciously and sub-consciously perceived visually degraded stimuli. Schurger and company offered the conjecture that the tighter clusters meant the neural representation was more robust. We interpret the effect as a stronger, more prominent signal and a decreased impact of noise. As such, an increase in SNR should have the effect of producing higher precision in neural representation.

1.4 The Effect of NE on Neural Representation

The spacing of clusters of network states representing a category of everyday objects, such as houses, should be influenced by both real variation in the representation of different pictures of houses, and by variation due to unrelated processing (noise). If NE enhances the SNR (reducing the influence of noise), then the cluster should get tighter as cortical levels of NE increase. Thus, we will manipulate NE levels pharmacologically with atomoxetine, with the hypothesis that the increased levels of cortical NE produced by atomoxetine (e.g. Bari & Aston-Jones, 2012) will be associated with more tightly spaced category clusters.

In addition, we will record pupillometry as a secondary measure of NE activity employed within each level of the psychopharmacological manipulation. Pupil diameter has been shown to closely track NE levels in the brain (Aston-Jones & Cohen, 2005), whereby smaller pupil diameter indicates lowers levels of tonic NE. Within each drug condition, we will rank trials according to average pre-stimulus pupil diameter, and divide them at the median. We expect that trials with greater pre-stimulus pupil diameter (associated with higher tonic NE) will have more tightly spaced category clusters than trials with small pre-stimulus pupil diameter.

1.5 The Effect of NE on Exploratory vs. Exploitative Behavior

According to a recently proposed theory (Aston-Jones & Cohen, 2005; Nieuwenhuis, Aston-Jones, & Cohen, 2005), the different modes of LC activity serve to regulate a fundamental tradeoff between two behavioral strategies: exploitation vs. exploration. Individuals must continually decide whether it would be better to pursue known sources of reward (exploitation), or whether there is more to be gained by searching for new strategies or opportunities (exploration). This dilemma in how we invest our time and effort is a well-known problem in the reinforcement literature.

High phasic/low tonic LC activity promotes exploitative behavior by facilitating processing of task-relevant information (via the phasic response),

while filtering out irrelevant stimuli (through low tonic responsivity). By increasing the phasic response of the LC, the cognitive system is better able to engage in the task at hand, and maximize rewards harvested from this task. In contrast, low phasic/high tonic LC activity promotes behavioral disengagement by producing a more enduring and less discriminative increase in responsivity. Although this degrades performance within the current task, it facilitates the disengagement of attention from this task, thus allowing potentially new and more rewarding behaviors to be emitted. Thus, the transition between the two LC modes can serve to optimize the trade-off between exploitation and exploration of opportunities for reward, and thereby maximizes utility.

Our proposed psychopharmacological increase in NE should be approximately equivalent to raising tonic levels of NE, thus inducing the low phasic/high tonic LC mode and promoting exploratory behavior. Our collaborators at Princeton University have designed two gambling tasks that elicit both exploratory and exploitative behavior in participants, and that allow quantitative assessment of instances of each type of behavior. We will have our participants complete these tasks outside of the fMRI scanner, after the primary (in-scanner) task has been completed. We will assess the degree to which subjects engaged in exploratory behavior under the influence of atomoxetine and compare that to the control (placebo) condition. We predict that subjects will exhibit significantly more exploratory behavior when under the influence of atomoxetine.

1.6 The Effect of NE on Biasing Neural Activity

The brain-wide increase in neural responsivity produced by increases in NE levels should have the impact of enhancing differences in strength between competing neural representations: Already strong representations should become stronger, while weaker, competing representations should become even weaker. It follows from this that biases in processing should be enhanced as NE levels increase. For example, Eldar and Niv recently demonstrated that when measures of pupil diameter suggest high levels of cortical NE, subjects demonstrate a stronger bias toward predisposed learning styles (2012) and a stronger bias toward attended versus unattended stimuli (manuscript in preparation); while Proulx and colleagues (Proulx & Heine, 2008; Proulx, Heine, & Vohs, 2010) have demonstrated that uncertainty, a factor thought to increase NE levels (e.g. Yu & Dayan, 2005), causes a stronger affirmation of a subject*s central, moral beliefs. We will investigate two of these ways in which NE effects should manifest in behavior.

First, subjects will read several short descriptions of crimes and heroic acts, and will be required to either set the monetary punishment for the crime (ticket amount) or the monetary reward for the heroic act. We expect these opportunities to affirm one*s moral beliefs will be influenced by NE levels whereby high NE under the influence of atomoxetine will result in more extreme values to be set as punishments and rewards compared to the placebo condition.

Second, subjects will have to identify an ambiguous letter embedded

within a three-letter string that forms a word when the ambiguous letter is interpreted as one of two possible letters, but does not form a word when the ambiguous letter is interpreted as the other possible letter. Eldar and Niv found subjects are less likely to be influenced by the irrelevant outer letters when pupil diameter suggests NE levels are high. We expect to observe this same effect when comparing subjects under the influence of atomoxetine versus placebo.

Study objective

The primary objective of this study is to measure the effect of a psychopharmacological manipulation of NE on fMRI measures of the fidelity of cortical representation.

The secondary objective is to determine if increased levels of cortical norepinephrine will be associated with more exploratory behaviour in a gambling task, as predicted by the adaptive gain theory of the LC-NE system.

The third objective is to determine if atomoxetine-enhanced noradrenergic activity will strengthen predispositions that may be associated with habitual and/or entrenched patterns of neural activity, as manifested by the interpretation of letters within three-letter strings and in answering questions related to the participant*s personal beliefs.

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 event-related fMRI data collection. Each subject will perform the task in the MRI scanner under the influence of atomoxetine in one session, and under the influence of a placebo in the other. The study will start in the EEG lab on the ninth floor of the LUMC (Psychiatry department), and move down to the fMRI room on the first floor about 112 minutes after the subject first arrives. Total scanning time will constitute approximately 41 minutes in each session, and the subject will return to the EEG room after being scanned. There are an additional 65 minutes of experiment tasks to perform outside of the scanner (in the EEG lab before and after the fMRI scanning). With breaks, time for explanations, for the drug to take effect and for moving between locations, each session will last approximately four hours. Participants will be administered the drug 75-80 minutes before the first experiment task to ensure that tasks are performed during peak blood levels (Chamberlain, Muller, Blackwell, Robbins, et al.,

2006; Graf, et al., 2011), and the final task will be completed 210 minutes (3 hours, 30 minutes) after taking the drug, within the window of time when the drug should still be having an effect on cognition (Sauer, Ring, & Witcher, 2005).

Drug Intervention
Participants will receive on one occasion 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, participants will receive a placebo pill.

Task 1
In the scanner, subjects view a series of isoluminant, monochromatic images of faces, houses, and cats, and are required to categorize each picture accordingly using one of three right-hand button-press responses. These categories of stimuli have been used successfully before in MVPA studies of visual categorization (e.g. Haxby et al., 2001; Schurger et al., 2010). Images will be presented in random order, and will be shown on screen for 1500 ms each, followed by a response screen displayed for two seconds asking the subject to indicate the category to which the picture belonged. After the two-second response screen, a fixation cross will be presented for an inter-stimulus interval varied randomly between 7500 ms and 9500 ms, averaging 8500 ms. This slow design is conducive to both our fMRI methods, and our pupillometry methods. Subjects will complete two blocks of 60 trials (120 in total), with a one-minute break between blocks. Each block will be 12 minutes in duration.

Task 2
Participants will play a series of gambling games where they select from one of two slot machines, with the goal of maximizing winnings. Each game involves two *new* slot machines with unknown pay-off probabilities, and starts with four *forced* trials where the program selects which slot machine to pull, with the subject accumulating winnings, and more importantly, accumulating information about the pay-off probabilities of the two slot machines based on those first four outcomes. After the forced pulls, the subject will get to make a variable number of additional free-choice pulls: Either one free-choice pull, six, or eleven, depending on the game. Subjects will complete 150 games, with each taking an average of 12 seconds to complete, for a total duration of 30 minutes. Participants will then complete a second, continuous-game version of this task that is not divided between different games but instead contains random *change points* where the underlying probabilities of the slot machine

changes without any cue to the participant. This second version takes approximately 15 minutes to complete. Subjects score points during these tasks and will receive a monetary bonus at the end of the tasks that varies linearly with the amount of points scored, ranging from 0 Euros to 6 Euros.

Task 3
Participants will be instructed to identify an ambiguous central letter embedded within a three-letter string, while ignoring the outside letters. The identity of the central letter will be ambiguous, created by morphing one letter to look like another letter. For example, the letter *H* can be made to look more like the letter *A* by angling the top vertical lines of the *H* toward the center. Critically, on each trial, one of the two letters used to create the morph will fit with the outer letters to make a common three-letter word, whereas the other letter would not form a real word. For example, the A/H morph could appear with outer letters to seemingly form the word *THE* or the word *DAY*, whereas in contrast *TAE* and *DHY* are not real English words. These letter strings are preceded by a subliminal prime (33 ms) which is either semantically related or unrelated to the real-word interpretation of the letter string. The letter string is then presented for 225 ms, followed by a response screen presented for 5000 ms. Subjects are instructed to concentrate only on the shape of the central letter and ignore the influence of the outer letters. They indicate which letter the central letter looks most similar to by choosing from a list of four letters, two of which are the two letters used to create the morph. Subjects will perform 88 trials of this task, for a total duration of approximately eight minutes.

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:	Observational non invasive
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-05-2013
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	03-04-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-05-2013

Application type:	Amendment
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	NL43339.058.13