The role of the noradrenaline and acetylcholine systems in uncertainty estimation and temporal attention

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Primary Objective: to ascertain whether administered clonidine and scopolamine affect performance (as measured by modulation of reaction times, learning and/or error rates) in a range of cognitive tasks designed to examine uncertainty estimation and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39477

Source
ToetsingOnline

Brief title
Neuromodulation and uncertainty

Condition

- Other condition

Synonym
niet van toepassing

Health condition

het onderzoek is van algemeen cognitief-psychologische aard en heeft geen betrekking op stoornissen of aandoeningen.

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: NWO;Open Competitie-toekenning aan dr. Sander Nieuwenhuis

Intervention

Keyword: Clonidine, Scopolamine, Temporal attention, Uncertainty

Outcome measures

Primary outcome

The main study parameters are cognitive task performance as reflected by reaction times and error rates, in addition to EEG measurements. The endpoints are the modulatory effects of clonidine and scopolamine relative to placebo on the main study parameters.

Secondary outcome

Secondary study parameters are individual differences as operationalised by genotyped polymorphisms and participants* scores on personality questionnaires. The endpoints are correlations and statistical analyses with the results from the genetic analyses and with questionnaire scores.

Study description

Background summary

There are striking commonalities in the anatomical organization and low-level actions of different neuromodulator systems, as well as direct interactions between these systems (Briand et al., 2007). An important goal for cognitive neuroscientists is to delineate the specific contributions of particular neuromodulator systems to cognitive control and decision making. The primary objective of the proposed research is to take a step toward that goal by examining and comparing the involvement of the noradrenaline (NA) system and acetylcholine (ACh) system in representing various forms of uncertainty

associated with a given behavioral context.

There are strong reciprocal interactions between the NA and ACh systems (Briand et al., 2007), and they apparently contribute in a similar way to alerting and arousal functions. In line with this view, a recent computational model of Yu and Dayan (2005; Dayan & Yu, 2006) proposes that NA and ACh have specific but complementary roles in coding uncertainty. According to this model, ACh is involved in signaling expected uncertainty, which arises from known unreliability of predictive relationships within a familiar environment. In contrast, NA is proposed to be involved in reporting unexpected uncertainty, induced by gross changes in the environment that produce sensory observations that strongly violate top-down expectations. Yu and Dayan (2005) review a number of pharmacological studies that have manipulated either NA or ACh levels and have examined only one type of uncertainty. We intend to replicate some of these key observations underlying the model, but in the same participants in a task that manipulates both expected and unexpected uncertainty.

Recent research has demonstrated the critical involvement of the NA system in the generation of the P300 (or P3) component of the event-related potential (Nieuwenhuis et al., 2005), a well-known neural correlate of estimated phasic uncertainty signals (Nieuwenhuis, in press). There is also substantial evidence for an influence of the ACh system on P3 generation (Wang et al., 1997; Hammond et al., 1987). However, the relative contributions of these two neuromodulator systems to the generation of the P3 are not well understood. The goal of this experiment is to test a hypothesis proposed by Ranganath and Rainer (2003). Their hypothesis is that the two neuromodulator systems contribute to separate subcomponents of the P3: the P3a (or novelty-P3) and the P3b. The P3b has a parietocentral scalp distribution and is mainly sensitive to infrequent task-relevant stimuli. The P3a has a prominent frontocentral scalp distribution and is mainly sensitive to novel and highly deviant or salient task-irrelevant stimuli. Most P3s are a mixture of these two subcomponents (Spencer et al., 2001). Ranganath and Rainer discuss one study that found that administration of a NA antagonist in monkeys selectively abolished the posterior P3b, but left the frontal P3a unaffected. By contrast, in another study, administration of an ACh antagonist in humans attenuated the P3a but not the P3b. These findings suggest that the NA system may primarily affect the P3b, whereas the ACh system may primarily affect the P3a. Indeed, the topography of cortical generators of the P3a and P3b seems consistent with the primary projection areas of the basal forebrain (i.e., ACh: frontal and anterior medial) and locus coeruleus (i.e., NA: parietal). However, note the apparent contradiction between this hypothesis and the model by Yu and Dayan (2005) that we discussed above: novel and other unexpected stimuli (ACh: P3a) seem a source of unexpected uncertainty, whereas infrequent task-relevant stimuli (NA: P3b) seem a source of expected uncertainty! Our intended experiment allows us to contrast these two hypotheses by pharmacologically manipulating NA and ACh activity in participants.

Another important objective of the proposed research is to examine the role of

the NA and ACh systems in temporal attention. If a visual target stimulus is immediately preceded by a salient yet task-irrelevant auditory stimulus, a participant*s reaction time to the target is significantly decreased (Bernstein, Clark, & Edelstein, 1969a; 1969b). Several researchers have proposed that this accessory stimulus effect may be related to the NA system (Hackley, 2009; Jepma et al., 2009; Stafford & Jacobs, 1990). According to this view, the locus coeruleus (or LC), the major source of noradrenergic innervation of the forebrain (Berridge & Waterhouse, 2003) is activated by the saliency of the accessory stimulus, which in turn boosts activity in the motor cortex through phasic NA release, thus speeding up the response. We will test this hypothesis by examining the effects of pharmacologically decreasing NA activity on the accessory stimulus effect, and comparing this with the accessory stimulus effects associated with decreased ACh (drug control) and placebo.

Another major paradigm for studying temporal attention is the attentional blink task, in which participants are instructed to identify two targets (e.g. numbers) in a rapidly presented series of distractors (e.g., letters). If these two targets are presented in rapid succession, participants are often unable to identify the second target (i.e. they exhibit an *attentional blink*). Theoretical work has suggested that the attentional blink reflects the temporal dynamics of LC activity and consequent effects on NA activity (Nieuwenhuis et al., 2005b). We will test this account by examining the effects of a NA manipulation on attentional blink performance. This experiment will replicate earlier work by Nieuwenhuis et al. (2007), but with greater statistical power, a within-subject design, and other design improvements. Again, an ACh manipulation will serve as drug control.

There are large individual differences in the pharmacodynamics and cognitive effects of the drugs we intend to administer, which complicates an interpretation of the results. To capture these individual differences, it is necessary to collect information about gene polymorphisms that affect NA and ACh activity (Abbott, 2003). Personality questionnaires are another source of critical information about individual differences that can help explain the variance in drug effects on our experimental measures (e.g. Cools et al., 2005).

Study objective

Primary Objective: to ascertain whether administered clonidine and scopolamine affect performance (as measured by modulation of reaction times, learning and/or error rates) in a range of cognitive tasks designed to examine uncertainty estimation and temporal attention, as well as specific components of the EEG signal that will be used as neural correlates of specific cognitive constructs like uncertainty estimation.

Secondary Objective(s): to explore possible individual differences in the

behavioural and EEG indices of uncertainty estimation and temporal attention by means of genetic analyses and personality questionnaires. Several personality trait questionnaires will be used as psychological corroborations of the genetic analyses of polymorphisms. We will use a state questionnaire (the Visual Analogue Scales) to gain insight in participants* levels of sedation, but also in their current mood and how it is affected by clonidine and scopolamine. This allows us to chart the psychological effects of both drugs.

Study design

The proposed study uses a double-blind, pseudo-randomized, placebo-controlled double-dummy cross-over design. Due to different pharmacokinetic profiles of clonidine and scopolamine, the two drugs will be administered at different times relative to testing. Participants* EEG is measured in three sessions (each one week apart), once following administration of 150µg of clonidine verum (and scopolamine placebo), once following 1.2 mg of scopolamine verum (and clonidine placebo, and once following clonidine and scopolamine placebo, in a counterbalanced order. We will test 24 participants, four with each possible order of treatments.

While the EEG is measured, participants perform four cognitive computer tasks (lasting about 20 minutes each; cf. Section 7.3); prior to EEG measurements, participants complete a number of questionnaires (which will take less than an hour in total). One session will last about four hours and twenty minutes.

Intervention

Clonidine, 150 µg, single dose, administration p.o. in a capsule. Clonidine is a centrally acting adrenergic alpha-2 agonist that is used mainly as an antihypertensive drug, as well as a maintenance drug in cases of migraine. Clonidine is metabolized by the liver and has an elimination half-life of ranging from 5.6-12.3 hours (mean 7.7 hours; Keränen et al., 1978).The usual maintenance dose for antihypertensive indications is between 0.075 and 0.15 mg thrice a day; for migraine indications, usual maintenance doses are between 0.025 mg and 0.075 mg twice a day. We intend to administer a single oral dose of 0.2 mg clonidine, the most widely used dose in psychopharmacological research (e.g. Frith et al., 1985; Coull et al., 2001; Smith et al., 2003). Because of the anti-hypertensive properties of clonidine, heart rate and blood pressure will be monitored for subject safety. Measurements will be taken just prior to ingestion of the tablet, and then every 60 mins for the remainder of the experimental session.

Scopolamine hydrobromide, 1.2 mg, single dose, administration p.o. in a capsule. Scopolamine is a cholinergic muscarinic receptor antagonist that is used mainly as an anti-emetic and a treatment of intestinal cramping. Scopolamine is generally administered in one of two forms: as a transdermal

patch (indication: travel/motion sickness) or in *pure form* (as tablets or injections, mainly for research purposes, or occasionally as treatment for intestinal cramping). Because it is difficult to predict the pharmacokinetics of transdermal patches, researchers usually administer the pure-form scopolamine via enteral, intravenal, or intramuscular routes. Because oral administration is the least aversive method of administration, we have decided to give scopolamine tablets. A literature search has revealed that in cognitive research, scopolamine tablets are administered in doses that range from 0.15 to 1.2 mg; higher doses generally produce more pronounced cognitive effects without eliciting more adverse side-effects. Therefore, we intend to administer a single oral dose of 1.2 mg, which has measurable effects on cognitive function (e.g. Callaway et al., 1991; Parrott, 1986; Pompéia et al., 2002), and induces a similar level of sedation as 0.2 mg clonidine.

Note that participants do NOT receive BOTH clonidine and scopolamine during a single session of the study: these drugs are administered during separate sessions.

Study burden and risks

The number of on-site visits is three (plus a medical screening prior to participation); in one session placebo is administered; in a second session clonidine is administered, and in a third session scopolamine is administered. The risk of a single dose of either of these drugs is minimal, but to further minimize the remaining risk, participants will be screened for bradycardia and/or hypotension, as well as glaucoma. The presence of any of these conditions will preclude participation in the proposed study. Previous studies have used comparable or higher doses of these drugs without reporting adverse side-effects (e.g. Tiplady et al., 2005: 300 µg of clonidine; Callaway et al., 1991: 200 µg of clonidine and 1.2 mg of scopolamine). Saliva will be obtained from participants for a genetic analysis of specific polymorphisms related to activity of the noradrenaline and acetylcholine systems; this procedure is not painful and will take place in a secluded room to guarantee participants* privacy.

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

Adult participants between 18 and 30 years old, with no history of neurological disorder, hypotension, or glaucoma will be included in this study. All participants will be native Dutch speakers.

Exclusion criteria

Exclusion criteria are: hypotension, bradycardia, cardiac arrhythmia, severe pulmonary conditions, head trauma, learning disabilities, pregnancy, alcoholism or substance abuse, glaucoma, renal failure or hepatic insufficiency, or use of (psychotropic) medication that may affect the central nervous system. Smokers will be excluded because of the effects of nicotine on the cholinergic system.
A heart rate of less than 60 beats per minute and/or a blood pressure lower than 100/60 mmHg will lead to exclusion prior to the test phase.
For safety reasons (i.e. to ensure optimal communication between participants and experimenter), only native Dutch speakers will be included as participants.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-06-2012
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO

Date:	03-02-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	10-04-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	05-06-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	NL36542.058.11