The neurochemical basis of goal-directed behavior

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Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON46785

Source
ToetsingOnline

Brief title
The neurochemical basis of goal-directed behavior

Condition

- Other condition

Synonym
Psychiatric or neurological disorders such as schizophrenia and depression

Health condition

psychiatrische en neurologische stoornissen

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: Leiden Instituut voor Brein en Cognitie

Intervention

Keyword: [18F]-DOPA PET, Cognitive control, Dopamine, Noradrenaline

Outcome measures

Primary outcome

The main study parameters are the regional [18F]DOPA influx (Ki) values,

performance on computer tasks (typically accuracy and reaction time),

psychophysiological measurements of for example blink rate and pupil dilation,

self-reports using questionnaires, and structural & functional MRI.

Secondary outcome

See primary study parameters

Study description

Background summary

The aim of the current project is to enrich research on neurochemistry and goal-directed behavior conducted at the FSW and LUMC using neuro positron emission tomography (PET), and in doing so fill a pervasive gap in the literature on this behavior. Excellent goal-directed behavior is often considered a hallmark of human achievement over other animal species, leading a vast body of literature to examine why some of us are better or worse at certain aspects of this behavior, as well as how and why this behavior fails in the case of clinical disorders. While the neurobiology underlying goal-directed behavior is often speculated upon, it is notably ill-investigated as the majority of research relies on indirect measurement of this neurobiology, for example by using proxy measures such as genetics, or even foregoing such measurement entirely in favor of making only behavioral assessments. As a result, existing literature on neurochemistry and goal-directed behavior is burdened by pervasive use of indirect markers of neurobiological constructs, leading conclusions to be based on assumptions that are scarcely validated.

However, PET enables relatively direct measurement of specific neurotransmitter systems, and therefore allows us to correlate neurotransmitter function with behavioral-physiological assessments and validate their presumed associations. This contributes knowledge to several major fields of interest of Leiden University, such as neurochemical (dys)function in psychiatric and neurodegenerative disorders and healthy aging, and in particular the role of neurochemistry in the human potential for cognitive performance and well-being over the lifespan.

Study objective

In the present study we aim to test how individual differences in the catecholamines, i.e., highly influential neurotransmitters, dopamine (DA) and noradrenaline (NA) function are related to individual differences in goal-directed behavior in healthy individuals. To do so, we propose the following objectives:
The first main objective of this study is 1a. to examine whether striatal [18F]DOPA influx (Ki) values in healthy individuals are correlated with performance on tasks tapping into goal-directed behavior, such as task-switching and working memory paradigms. Secondary to this aim is 1b. to investigate whether regional [18F]DOPA influx (Ki) values predict brain functional and structural connectivity on the other hand, measured using 3 Tesla MRI scanning. Furthermore, the aim 1c. is to validate the relationship between DA and NA activity, indexed by regional [18F]DOPA influx (Ki) values, and presumed indirect makers of these neurotransmitters, such as spontaneous eye blink rate and pupil dilation. In addition, there are many inter-individual characteristics that are known to predict cognitive performance, such as heart rate variability, reward sensitivity and subclinical traits of psychosis and autism. This study aims to explore the neurochemical basis underlying these characteristics by determining whether they are correlated with individual differences in DA and NA function.
The other main objective of this study is to validate the effects of transcutaneous (through the skin) vagus nerve stimulation (tVNS), a safe, non-invasive and mild method of stimulation that transiently enhances NA activity in the brain. Behavioral studies are consistent with enhancement of NA-related performance during tVNS, but these studies lack any direct measurement of NA activity in relation to tVNS efficacy. As a concrete test of its mechanism-of-action, this study will examine whether behavioral response to tVNS, measured on cognitive computer tasks, is predicted by baseline NA activity, indexed by [18F]DOPA influx (Ki) values in the locus coeruleus.

Study design

Cross-sectional

Study burden and risks

Participants will be assessed on four separate occasions: (1) Screening, behavioral measurements (computer tasks, questionnaires), (2) tVNS and psychophysiological-behavioral measurements, (3) (f)MRI scan, and (4) PET/CT scan.
Regarding PET/CT scanning, the radiation dose of this study is 3.3 mSv and falls within category IIb (minor to intermediate). Nataf et al. (2006) performed 170 [18F]DOPA PET examinations for the detection of neuroendocrine tumors. A few of those patients reported a single, minor adverse effect. They experienced a light and transient burning sensation at the injection site. This was probably caused by the acidity of the radiopharmaceutical. To our knowledge, no other side effects have been reported.
Regarding (f)MRI scanning, there are no known risks associated with participating in an fMRI study. Numerous human subjects have undergone (f)MRI 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 scanner and in these cases the study will be terminated.
Regarding tVNS, the stimulation frequency, intensity and duration are within safety limits established from prior work in humans (Kreuzer et al., 2012). Previous studies have used comparable or higher tVNS stimulation frequency, intensity and duration without reporting adverse side-effects (Dietrich et al., 2008; Kraus, Kiess, Schanze, Kornhuber, & Forster, 2007). The stimulation is not painful, only a typical short-lasting skin sensation (i.e., itching and/or tingling) is experienced.
Benefits of the study: The results of this study will contribute greatly to our understanding of the neurobiology of goal-directed behavior. By looking directly at the individual synthesis capacity of catecholamines, we will better understand how and why individual differences in goal-directed behavior occur in the healthy population, which will also inform us of how disturbances in this neurobiology can explain failure of goal-directed behavior in patients with clinical disorders or even only subclinical symptoms. Furthermore, the results from this study serve as a critical and unprecedented validation of indirect markers of catecholamine function, such as blink rate and pupil dilation. These markers are pervasively used in studies of both healthy and clinical populations alike to predict behavioral assessments, and have been used as predictive factors for efficacy of cognitive enhancement techniques and as indicators for clinical diagnoses and treatment responsivity. However, large-scale, well-powered research validating the nature of these markers is extremely scarce if not non-existent, which severely undermines the interpretability of the existing literature. By validating these markers, this study will serve as a crucial reference for research that wishes to use these non-invasive and cost-efficient markers in studies of clinical and healthy populations. In doing so, our results are an important step toward creating treatments and cognitive enhancement interventions tailored to individual needs, which is of particular interest in an increasingly individualistic society that places high value and expectations on optimizing personal achievement. Although we only examine healthy individuals in this study, the

knowledge derived from this study is not restricted to the healthy population. It will also help us understand and predict how and why this behavior can fail in clinical disorders, which features (e.g. blink rate, pupil dilation) can predict self-reported, subclinical symptoms, which paves the way for establishing predictors of sensitivity to specific, targeted treatments. For example, if blink rate indeed positively predicts striatal dopamine activity, then depressive patients with a high blink rate might not benefit and instead even suffer from treatments targeted at enhancing striatal dopamine.

Contacts

Public
Universiteit Leiden

Wassenaarseweg 52
Leiden 2333 AK
NL
Scientific
Universiteit Leiden

Wassenaarseweg 52
Leiden 2333 AK
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age 18-30 years

Right-handed

Exclusion criteria

- History of psychoactive medication (e.g., antidepressants, antipsychotics, amphetamines)
- History of substance (ab)use (e.g., smoking, cannabis, XTC)
- History of psychiatric/neurological disorders (e.g., depression, epilepsy, ADHD)
- Eating or using caffeinated drinks during the period of six hours prior to any of the sessions
- Heart-related disorders
- Metal objects in or around the body.
- Participation in a scientific examination where radiation was used, in the last year
- Positive urine drug screen on the day of the PET/CT scan. Participants will be tested on cannabis, amphetamine, XTC, cocaine and opiates.
- In women: positive pregnancy test on the day of the PET/CT scan and lactation.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	80
Type:	Anticipated

Ethics review

Not approved

Date:	07-06-2018
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	NL64602.058.18