The impact of dopamine on functional and structural connectivity

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To investigate the effect of dopamine-related genetic polymorphisms on resting-state fMRI measures of network functional and structural connectivity.

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

Summary

ID

NL-OMON42846

Source
ToetsingOnline

Brief title
Dopamine and neural connectivity

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: Vidi

Intervention

Keyword: connectivity, dopamine, fMRI, genetics

Outcome measures

Primary outcome

~MRI data acquisition~

Following the approved protocol P13.282 *Norepinephrine and neural processing*, functional neuroimaging will be performed at the 3T fMRI scanner of the LIBC, located in the the LUMC. One resting state fMRI scan series for functional connectivity lasts approximately 8 minutes, whereas a series for structural connectivity lasts approximately 10 minutes. For registration purposes, one T1-weighted scan will be acquired for each subject.

~DNA samples~

Following the approved protocol FC02 *Fludrocortisone and depression-related cognition*, genetic profile will be determined by collecting mucus with buccal swabs, i.e. swabbing the inside of one*s cheek. Buccal swabs will only be used for the purposes described and will be stored at FSW at -20 °C after completion of the session until biochemical analysis takes place.

~Statistical analysis~

Results of each subject will be compared based on genotype, using analysis of variance. This approach permits detecting differences in resting-state brain activity and structural connectivity between individuals of different

genotypes.

Secondary outcome

n.v.t.

Study description

Background summary

Dopamine (DA) plays a key role in the regulation of human cognition. For instance, from a cognitive perspective DA is thought to modulate the balance between stable versus flexible cognitive representations, whereas from a biological perspective it is thought to regulate the interplay between the prefrontal cortex (PFC) and the striatum (Cools & D*Esposito, 2011). The importance of DA to everyday cognitive-behavioral functioning is illustrated by cases in which the DA system is severely dysregulated, for example in Parkinson*s disease (Dauer & Przedborski, 2003) and schizophrenia (Howes, McCutcheon, & Stone, 2015).

~Genetic variation in DA function~
Many studies have shown a crucial role for inter-individual differences in DA function. Such differences have been found to affect both cognition and the interplay between the PFC and striatum. So far, progress has been made in identifying genetic markers that can account, in part, for these differences.
In particular, the enzyme catechol O-methyltransferase is responsible for degradation of DA in the PFC (Karoum, Chrapusta, & Egan, 1994), whereas the DA transporter (DAT) is responsible for DA reuptake in the striatum (Sesack, Hawrylak, Matus, Guido & Levey, 1998). Variations in the COMT and DAT genes are known to affect prefrontal and striatal DA levels, respectively, and have received increasing attention as possible modulators of cognitive control functions (Cools & D*Esposito, 2010). Common variations in the DAT gene are 9 and 10-repeat alleles, which are associated with higher and lower striatal DA level, respectively. On the other hand, common variations in the COMT gene are a substitution of a Met for a Val allele, with Met carriers having higher prefrontal DA levels than Val carriers. In light of this information it is interesting to note that Bertolino et al. (2006) showed that these polymorphisms, while targeting one specific area, can modulate the function of both the PFC and striatum. Their findings indicated that brain-activation patterns of individuals with putatively low striatal DA (10-repeat carriers of DAT) resembled that seen in subjects with putatively high prefrontal DA levels (Met carriers of COMT).
In the present study we wish to extend these findings by investigating the effects of DA-related gene polymorphisms (COMT, DAT) not only on structural

connectivity in the brain but functional connectivity as well. Structural connectivity is assessed using diffusion tensor imaging (DTI), which quantifies the density of white matter tracts. In light of the aforementioned findings by Bertolino et al. (2006), we expect that carriers of the 9-repeat allele of the DAT gene, who have higher striatal DA, will have increased white matter connectivity in the striatum, relative to 10-repeat allele carriers and Met carriers of COMT. Further, we will assess functional connectivity using resting-state brain-activation patterns, and we expect that individuals with a genetic predisposition towards higher striatal activation will concurrently have lower PFC activation.

Study objective

To investigate the effect of dopamine-related genetic polymorphisms on resting-state fMRI measures of network functional and structural connectivity.

Study design

~Design~
The proposed study will use a between-subjects design, with genotype as between-subjects factor.

~General procedure~
The proposed study will consist of one session of fMRI data collection. The study is carried out in the fMRI room on the first floor. Upon arrival buccal swabs are used to collect genetic material. fMRI data collection will take approximately 30 minutes per session, during which both functional and structural connectivity is assessed.

~Session time line~

Session 1
-20 min. Arrival 5 min.
-15 min. Collect DNA via buccal swabs 5 min.
-10 min. Transfer to fMRI room / change into MRI clothes 10 min.
0 min. MRI: T1 and resting state 30 min.
30 min. Subject leaves scanner 5 min.
35 min. Debriefing 5 min.
40 min. End of experiment

60 min. total duration

Study burden and risks

There are no known risks associated with participating in an fMRI study. Numerous human subjects have undergone 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 immediately at the subject's request.

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 right-handed subjects, who have no personal relationship with the researchers. Female subjects will be taking hormonal contraceptive medication to limit fluctuations in dopamine function associated with the menstruation cycle

Exclusion criteria

Significant history of head trauma, learning disabilities, neurological or psychiatric illness, use of anti-depressants or psychotropic medication, and possible pregnancy (in adult females).
Smoking, to avoid nicotine withdrawal effects during the study.
MRI contra-indications, including metal implants and claustrophobia.
Alcohol consumption < 24 hours before drug intake, caffeine consumption < 3 hours before drug intake

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2016
Enrollment:	160
Type:	Anticipated

Ethics review

Approved WMO

Date:	25-08-2016
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	NL57592.058.16