DRD4 genotype as a moderator of L-Dopa intervention effects on parent-related neurocognitive processes, behaviors, and attitudes: A micro-trial of differential susceptibility to pharmacological intervention

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

Summary

ID

NL-OMON40955

Source
ToetsingOnline

Brief title
Differential susceptibility to L-Dopa in caregiving

Condition

- Other condition

Synonym
not applicable

Health condition

none, the study is not a clinical trial, participants are healthy young adults

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: Research grant from the Jacobs Foundation (CHF 120.000)

Intervention

Keyword: Caregiving, Differential susceptibility, Dopamine, Neurocognition

Outcome measures

Primary outcome

The study parameters of phase 1 are:

- Empathic responses: The participant will play a ball tossing game with three other (computerized) players. After a period of fair play, one of the fellow players will be excluded by the other 2 computerized players. We measure the change in the frequency of throws made by the participant to the excluded player.

- Prosocial behavior: At the end of the laboratory visit, participants will be shown a promotional UNICEF video asking them to make a donation (a money box is positioned next to the screen). We measure the amount of money donated. (All donations will be transferred to the UNICEF bank account after completion of the study.)

The study parameters of phase 2 are:

- Resting frontal asymmetry. Participants* resting EEG will be recorded and an

asymmetry index will be computed. We will investigate whether resting frontal alpha asymmetry can be considered an endophenotype for differential susceptibility.

- Neural indices of the processing of and attention to infant faces and sounds. ERP components indicative of processing depth and attention will be computed from the EEG recorded while participants listen to infant sounds and view infant faces. EEG asymmetry in response to faces and sounds, as a measure of approach-withdrawal responses to these stimuli, will also be computed. We will study effects of L-Dopa on these neural indices, and investigate whether L-Dopa effects are moderated by the DRD4 genotype and resting frontal asymmetry. In addition, we will investigate whether changes in neural indices after L-Dopa administration mediate changes in behavioral measures (sensitivity, interpretation of infant cues, caregiving attitudes, empathy).

- Cardiac indices of arousal in response to infant faces and sounds. Cardiac indices indicating sympathetic and parasympathetic activity will be computed from the ECG and ICG recorded while participants listen to infant sounds and view infant faces. We will study effects of L-Dopa on these neural indices, and investigate whether L-Dopa effects are moderated by the DRD4 genotype and resting frontal asymmetry. In addition, we will investigate whether changes in cardiac indices after L-Dopa administration mediate changes in behavioral measures (sensitivity, interpretation of infant cues, caregiving attitudes, empathy).

-Mirror-neuron activity. Mirror-neuron activity will be studied using measures derived from the EEG. We will investigate whether potential effects of L-Dopa

on these measures are moderated by the DRD4 genotype and resting frontal asymmetry. In addition, we will investigate whether changes in mirror-neuron activity after L-Dopa administration mediate changes in behavioral measures (sensitivity, interpretation of infant cues, caregiving attitudes, empathy).

- Sensitivity of caregiving behavior. The Leiden Infant Simulator Assessment will be used to measure participants* sensitivity. We will investigate investigate whether potential effects of L-Dopa on sensitivity are moderated by the DRD4 genotype and resting frontal asymmetry.

- Interpretation of infant cues. An infant-face version of the Reading the Mind in the Eyes Test will be used to measure participants* interpretation of infant cues. We will study effects of L-Dopa on this measure, and investigate whether L-Dopa effects are moderated by the DRD4 genotype and resting frontal asymmetry.

Secondary outcome

- Early life experiences. With respect to differential susceptibility it is important to take early experiences into account: In order to conclude that the DRD4 genotype conveys differential susceptibility, those carrying the 7-repeat allele should not only be more affected by the intervention (L-Dopa administration), and perform *best* under favorable conditions, but also do *worst* under unfavorable circumstances. As DRD4 genotype has repeatedly been observed to moderate effects of parenting experiences (see e.g., 1), we expect that under placebo conditions carriers of the 7-repeat allele with relatively unfavorable childhood experiences will do worst (i.e., show the least favorable scores on caregiving behavior and the least attention and approach responses to

infant stimuli), whereas under DA conditions carriers of the 7-repeat allele

with relatively favorable experiences will do best (i.e., most favorable

caregiving scores, and most attention and approach).

Study description

Background summary

The proposed study is a comprehensive micro-trial of dopamine-system mediated differential susceptibility in the realm of caregiving behavior. We first aim to investigate whether the dopamine receptor D4 (DRD4) genotype confers differential susceptibility to the effects of early life stress in a large sample of adults, in accordance with a meta-analysis that showed similar effects in children. We then aim to investigate more specifically whether DRD4 genotype confers differential susceptibility to effects of a dopaminergic pharmacological intervention (L-Dopa administration) on caregiving-related neurocognitive processes, behaviors, and attitudes. In addition, we examine whether frontal asymmetry can serve as an endophenotype for differential susceptibility. Because the analysis (and use) of genetic material is (relatively) time-consuming and expensive, and surrounded by ethical concerns and objections, and because multiple genes may be involved in conveying susceptibility (although a single gene might be an excellent proxy for a genetic pathway), obtaining an endophenotype for susceptibility would be worthwhile. Resting frontal asymmetry may be such an endophenotype, and it can be measured easily and non-invasively, and measures are relatively cheap. Finally, rigorous statistical probing will be conducted, including the use of simulations to test the integrity of the data. Results of these statistical assessments will be used to correct the data accordingly. These analyses will help to improve the quality of data-analysis and conclusions, and provide statistical guidelines for future data-analysis of similar designs.

Study objective

The study consists of two phases. In the first phase, we aim to investigate whether the dopamine receptor D4 (DRD4) genotype confers differential susceptibility to the effects of early life stress on empathy and prosocial behavior more generally in a large sample of adults. The second phase will be a more thorough test of differential susceptibility in the realm of more specific empathic and social behavior, i.e. caregiving. In this phase, we aim to investigate whether DRD4 genotype and resting frontal asymmetry confer differential susceptibility to effects of a dopaminergic pharmacological intervention on caregiving-related neurocognitive processes, behaviors, and

attitudes. Rigorous statistical probing will be conducted, including the use of simulations to test the integrity of the data, and results of these statistical assessments will be used to correct the data accordingly.

Phase 1 addresses the following questions:
1. What is the relationship between early life experiences, and adult empathy and prosocial behavior, and does DRD4-genotype moderate this effect?

Phase 2 addresses the questions:
2. What is the effect of L-Dopa administration (a pharmacological intervention that heightens levels of dopamine) on parenting-related neurocognitive processes, behaviors, and attitudes?
3. Does the DRD4 genotype moderate the efficacy of the pharmacological intervention?
We expect effects of L-Dopa administration to be more pronounced in carriers of the 7-repeat allele.
4. Can resting frontal asymmetry serve as an endophenotype for differential susceptibility?
5. Does measurement imperfection dilute or mask statistical main effects or interaction effects of genes and intervention?
6. Can knowledge about dilution or masking of effects be used to correct for it in order to improve the quality of substantive results?
We expect to produce reference material (e.g. look-up tables) to correct results from common analyses, using the fact that different types of variables have rather constant error rates.

Study design

Study design: The first phase of this study will involve recruitment of 600 individuals, who will be asked to provide a DNA sample and will fill out a questionnaire on common background variables (age, education), as well as early life experiences (early parenting, neglect, and abuse). To study the role of genotype and early experience on prosocial behavior and empathy, the participants will be asked to perform two brief laboratory computer-based tasks. DNA samples will be collected through a salivary DNA collection kit Oragene® 110 (DNA Genotek).
The second phase of the study will use a subset of the participants (n=200). The experimental procedure will be a double-blind, randomized placebo-controlled trial with a within-subject design. These participants will participate in two identical laboratory sessions at the Department of Child and Family studies, separated by approximately 4 weeks. L-Dopa will be administered orally shortly before one session and a placebo shortly before the other. The order of administration (L-Dopa first or placebo first) will be counterbalanced across participants To study the role of the DRD4 receptor in differential susceptibility to L-Dopa administration, groups of 7-repeat carriers and non-carriers will be compared. The data collection is expected to take

approximately 12 months.

Intervention

Participants will receive a fixed dose of 100 mg levodopa combined with 25 mg of carbidopa (Sinemet, Tmax1*445 min, half-time1*41-2 h), or placebo. A PET study in healthy volunteers demonstrated that a single dose of Sinemet changes DA levels in the putamen and caudate 1 h after intake.

Study burden and risks

Potential risk related to the study is negligible. A dose of 100 mg levodopa combined with 25 mg of carbidopa (Sinemet) will be administered orally shortly before one session and a placebo shortly before the other. Although chronic use of Sinemet can have considerable side-effects, a single dose of 100 mg levodopa combined with 25 mg of carbidopa has been used and found safe in several previous psychological studies. Saliva will be collected once to be used for genotyping. Collecting saliva is easy and almost effortless (participants just spit into a tube). The computerized tasks administered during the block of neurocognitive assessments (lasting about 30 minutes in total) require the participant to concentrate, but are otherwise simple and require minimum effort. The measurement of EEG and cardiac data is risk-free and non-invasive. There will be a 15-minute break after this block to allow the participants to relax and drink something. The behavioral tasks and questionnaires likewise require the participant to be alert and active, but are not physically or emotionally demanding, and participants will hardly notice the video-recording.

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, female, 18 years old or older, of caucasian descent

Exclusion criteria

pregnancy, breastfeeding, drug or alcohol abuse, prior psychiatric or neurological disorder,use of medication (except oral contraceptives), existing medical condition

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	30-01-2015
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Levodopa/carbidopa 100/25 PCH
Generic name:	Levodopa/carbidopa
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-05-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-10-2014
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
EudraCT	EUCTR2014-000206-36-NL
CCMO	NL47825.058.14

Study results

Date completed:	04-04-2017
Actual enrolment:	134