Dopaminergic Functioning in Autism Spectrum Disorder

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Developmental disorders NEC
Study type	Interventional

Summary

ID

NL-OMON47274

Source
ToetsingOnline

Brief title
Dopaminergic Functioning in Autism Spectrum Disorder

Condition

- Developmental disorders NEC

Synonym
Autism, Autism Spectrum Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Rivierduinen
Source(s) of monetary or material Support: GGZ Rivierduinen

Intervention

Keyword: [18F]-DOPA PET, Autism, Dopamine, Social defeat

Outcome measures

Primary outcome

Parameters for the first main objective (1a): [18F]DOPA influx (Ki) value and

Degree of loneliness (UCLA Loneliness Scale) in patients with ASD.

Parameter for the second main objective (1b): [18F]DOPA influx (Ki) value in

patients with ASD and healthy control participants.

Secondary outcome

Secondary study parameters are other self-report approximations of social

defeat, used in the secondary objectives 2a and 2b:

1. Degree of ostracism (OES-A).

2. Extent of perceived informal support (ISEL)

3. The desire for acceptance and belonging (Need to belong scale)

4. Degree of exposure to bullying before age 17 (Amended bullying

questionnaire)

5. Size of social network (LSNS)

6. Degree of loneliness (UCLA Loneliness Scale)

The number of sub-clinical psychotic experiences are measured using the PQ-16

(objective 2d).

Other parameters include covariates that might influence dopamine synthesis:

age, sex, smoking status.

Additionally, we will explore the possible confounding effects of factors that

might influence dopamine synthesis and/or social exclusion, such as ADHD

symptoms (ADHD Rating Scale-IV), socioeconomic status (BSMSS), childhood trauma

(JTV), depression (BDI-II), and anxiety (STAI-T).

Study description

Background summary

The social defeat hypothesis posits that long-term exposure to the experience of social defeat (SD) or social exclusion (SE) may lead to increased activity and/or sensitisation of the mesolimbic dopamine (DA) system and thereby increase the risk for psychosis/ schizophrenia. The hypothesis may explain the increased risk for migrants from non-Western countries, individuals with hearing impairment, low IQ, a history of childhood trauma or a non-heterosexual orientation. A single-photon emission computed tomography (SPECT) study tested this hypothesis in young adults with a serious hearing impairment (SHI) and obtained evidence of DA sensitization in these individuals, because administration of amphetamine led to a greater striatal dopamine release than in age-matched normal controls. Individuals with Autism Spectrum Disorder (ASD) are also vulnerable to social exclusion and at a greatly increased risk to develop psychosis/schizophrenia. The purpose of this study is to examine whether the mesolimbic DA system of non-psychotic individuals with ASD is also sensitized and whether sensitization correlates with social exclusion. Furthermore, we want to examine if patients with ASD have a higher striatal dopaminergic activity than healthy controls. To avoid the precipitation of a psychosis by the administration of amphetamine, it is proposed to conduct a [18F]DOPA positron emission tomography/computed tomography (PET/CT) study.

Study objective

The first main objective of this study is 1a. To examine whether striatal [18F]DOPA influx (Ki) values in non-psychotic individuals with ASD are positively related with the total score on the UCLA Loneliness Scale.
The second main objective of this study is 1b. To examine whether non-psychotic individuals with ASD have increased striatal [18F]DOPA influx (Ki) values compared to healthy participants.

Secondary objectives will be to test the following hypotheses:
2a. In non-psychotic individuals with ASD, striatal [18F]DOPA influx values are positively related to more experiences of being ostracized (OES-A), a greater discrepancy between the need to belong to others and the perceived availability of informal support (i.e., a combination of high scores on the Need to Belong Scale and low scores on the ISEL), a greater severity of bullying experienced before age 17 (Amended Bullying Questionnaire), and a smaller social network

(LSNS). The purpose of this is to relate other approximations of social defeat (besides loneliness, see objective 1a) to pre-synaptic striatal dopamine synthesis.
2b. Compared to healthy participants, non-psychotic individuals with ASD experience more loneliness (UCLA Loneliness Scale), feelings of being ostracized (OES-A), a greater discrepancy between the need to belong to others and the perceived availability of informal support (i.e., a combination of high scores on the Need to Belong Scale and low scores on the ISEL), a greater severity of bullying experienced before age 17 (Amended Bullying Questionnaire), and a smaller social network (LSNS). The purpose of this is to put the results of 1b in perspective: how socially defeated are individuals with ASD compared to healthy participants?
2c. Striatal [18F]DOPA influx values in the associative subdivision of the striatum correlate with measures of social exclusion, not similar values in other striatal areas.
2d. Striatal [18F]DOPA influx values correlate with the number of sub-clinical psychotic experiences (PQ-16).

Study design

Cross-sectional.

Intervention

Not applicable.

Study burden and risks

Benefits of this study:
- The study will contribute to our understanding of the aetiology and neurobiology of psychosis among people who have been socially excluded or defeated. The first step towards prevention is understanding the biological mechanisms underlying the increased risk for defeated individuals. If the results of this study are positive and confirmed by other studies, the development of drugs to stabilize the mesolimbic dopamine system and thereby prevent the development of psychosis, is urgently required. Furthermore, mental health treatment of patients at risk for psychosis, can be focused on reducing the social exclusion.
- The study may clarify the mechanism whereby people with ASD develop psychotic disorders.
- Participants who are found to be clinically at ultra-high-risk for psychosis and participants with high [18F]DOPA influx (Ki) values (upper quartile) may benefit, because they will be offered CBT, which halves risk for psychosis within period of 18 months.

Risks of this study:

- 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.
- The radiation dose of this study is 3.3 mSv and falls within category IIb (minor to intermediate). See Appendix K6 for a detailed description of the radiation dose and accompanying risks.

To avoid the precipitation of a psychosis by the administration of amphetamine, it is proposed to conduct a [18F]DOPA PET study without amphetamine.

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

1. DSM-5 diagnosis of Autism Spectrum Disorder (Patients only, for controls this is an exclusion criterion, see below).
2. Age: 18-30 years.

Exclusion criteria

1. DSM-5 diagnosis of Autism Spectrum Disorder (Healthy controls only)
2. Autism Spectrum Disorder due to a known organic disorder (*Syndromal ASD*, e.g., due to Fragile X syndrome, Klinefelter syndrome, 22q11 deletion syndrome).
3. Neurological disorder (e.g., epilepsy) or evidence of brain damage.
4. History of meningitis.
5. Intellectual disability (IQ<85).
6. Non-affective Psychotic Disorder or Bipolar Disorder (DSM-5: 297.1, 298.8, 295.40, 295.90, 295.70, 292.9, 291.9, 293.81, 293.82, 293.89, 298.9, 296.89, 303.13, 293.83, 296.89, 296.80, 296.4x, 296.5x, 296.7).
7. Social exclusion due to other causes than ASD: visible ethnic minority status, serious physical disability, serious visual or hearing impairment; at discretion of the researcher.
8. Current use of drugs (XTC, cocaine, etc.). Use of cannabis is allowed, but should have been stopped at least one month before the study. Cannabis abuse earlier in life is not allowed.
9. Alcohol- or drug abuse or dependence (DSM-5).
10. Use of an antipsychotic (ever) if prescribed for a psychotic disorder, as a former psychotic disorder is an exclusion criterion. Occasionally, antipsychotics are prescribed against e.g. anxiety or aggression. In these cases:
a) Incidental former use of antipsychotic is allowed, if last use has been more than a year ago.
b) Regular former use of antipsychotic is allowed, if last use has been more than two years ago.
c) Antipsychotic formerly administered as depot medication is allowed, if last injection has been more than two years ago.
11. Use of the antipsychotic quetiapine (ever), if prescribed in relation to a psychotic disorder. However, quetiapine is often prescribed against sleep difficulties and has a low affinity to dopamine receptors. In these cases:
a) Consumption is allowed if previously consumed in a low dose (*50mg), but last use has been more than 3 months ago.
b) Consumption is allowed if previously consumed in a high dose (>50mg), but last use has been more than 6 months ago.
12. Current use of ADHD medication (e.g. methylphenidate). Individuals who have stopped using these drugs for at least one year can participate in the study.
13. Current use of benzodiazepine or promethazine, unless last use has been more than 1 month ago.
14. Current use of other psychotropic drugs. Individuals who have stopped using the drugs for at least 3 months can participate in the study.

15. Smoking during the period of three hours prior to the PET/CT scan and eating or using caffeinated drinks during the period of six hours prior to the PET/CT-scan.
16. Participation in a scientific examination where radiation was used, in the last year.
17. Positive urine drug screen on the day of the PET/CT scan. Participants will be tested on cannabis, amphetamine, XTC, cocaine and opiates.
18. In women: positive pregnancy test on the day of the PET/CT scan and lactation.
19. Metal objects in or around the body.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-06-2017
Enrollment:	69
Type:	Actual

Ethics review

Approved WMO

Date:	05-07-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	06-04-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-04-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL54244.058.15