Dopaminergic Functioning in Autism Spectrum Disorder

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Primary hypotheses: 1a. Striatal [18F]DOPA influx (Ki) values in non-psychotic individuals with ASD are positively related to the total score on the UCLA Loneliness Scale (as an approximate measure of social defeat). 1b. Non-psychotic individuals...

Ethische beoordeling Status	Positief advies Werving gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON21453

Bron NTR

Verkorte titel Dopamine ASD

Aandoening

Autism Spectrum Disorder Autisme Spectrum Stoornis Social Defeat Social Exclusion Sociale Uitsluiting Psychosis Psychose Dopamine

Ondersteuning

 Primaire sponsor: GGZ Rivierduinen Leiden, Leiden University Medical Center (LUMC), Maastricht University
Overige ondersteuning: GGZ Rivierduinen Leiden, Leiden University Medical Center (LUMC), Maastricht University

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

1. Relation between [18F]DOPA influx (Ki) value and total score on UCLA Loneliness Scale (v3) in non-psychotic individuals with ASD.

2. The [18F]DOPA influx (Ki) value in non-psychotic individuals with ASD compared to the [18F]DOPA influx (Ki) value in healthy control participants.

Toelichting onderzoek

Achtergrond van het onderzoek

Background

The social defeat hypothesis of psychosis posits that long-term exposure to the experience of social exclusion may lead to increased baseline activity and/or sensitisation of the mesolimbic dopamine (DA) system and thereby increase the risk for psychotic disorders. According to this hypothesis, social defeat may be the common denominator for many risk factors for psychotic disorders (e.g., migration, impaired hearing, low intelligence, history of trauma, non-heterosexual orientation). The relation between social defeat and DA sensitization has been tested in a single-photon emission computed tomography (SPECT) study, which found evidence of DA sensitization in a group of young adults with a serious hearing impairment (Gevonden et al., 2014). Similarly, studies using positron emission tomography (PET) reported evidence for increased DA sensitization in adults who experienced more childhood adversity (Oswald et al., 2014; Egerton et al., 2016) and in migrants (Egerton et al., 2017).

Individuals with autism spectrum disorder (ASD), characterized by deficits in social communication and social interaction, are also at increased risk for psychotic disorders (Selten et al., 2015; Schalbroeck et al., in prep.). Due to the nature of their deficits, these individuals also experience more social exclusion. However, it is currently unknown whether social exclusion leads to enhanced DA activity in these patients, which may be the potential mechanism behind their increased risk for psychosis.

In the present study, we aim to test the social defeat hypothesis in individuals with ASD, examining whether the social exclusion that these individuals experience is related to an

increase in DA activity. A dynamic 90-min positron emission tomography (PET) scan will be used to image pre-synaptic striatal dopamine uptake after intravenous administration of [18F]DOPA (150 MBq). The main aims of the present study are two-fold. First, we examine whether greater loneliness (as an approximate of more social defeat) correlates to greater striatal [18F]DOPA influx (Ki) values. Second, we examine whether patients with ASD, who experience more social defeat, show greater striatal [18F]DOPA influx (Ki) values than a healthy control sample from the general population.

Study population

Individuals aged 18-30 years old, who never developed a psychotic disorder, will be eligible to participate (see sections above for the full list of In- and Exclusion criteria). Patients with ASD (n=45) will be recruited via Dutch mental health care institutes, universities, the Dutch Autism Association (Nederlandse Vereniging voor Autisme), and other institutes providing services to individuals with ASD. Healthy controls (n=24) will be recruited at universities and via advertisements in the local media. Patients with ASD and healthy controls will be matched on age, sex and smoking habits.

Statistical analysis

Separate multivariable linear regression analyses will be conducted to examine the study aims related to [18F]DOPA influx (Ki) values, social defeat (loneliness), and group (ASD patient or healthy control). Analyses will be adjusted for age, sex, and smoking. Statistical test assumptions will be checked prior to conducting the analyses.

Doel van het onderzoek

Primary hypotheses:

1a. Striatal [18F]DOPA influx (Ki) values in non-psychotic individuals with ASD are positively related to the total score on the UCLA Loneliness Scale (as an approximate measure of social defeat).

1b. Non-psychotic individuals with ASD have increased striatal [18F]DOPA influx (Ki) values compared to healthy control participants.

Secondary hypotheses:

2a. In non-psychotic individuals with ASD, greater striatal [18F]DOPA influx (Ki) values are related to other approximates of social defeat:

- More reports of being ostracized (OES-A)
- Greater severity of bullying experienced before age 17 (Bullying Questionnaire)

- Greater discrepancy between the need to belong to others (Need to Belong Scale) and the perceived availability of informal support (ISEL) (i.e. relatively lower perceived availability of support compared to their need to belong)

- Smaller social network (LSNS)

2b. Compared to healthy participants, non-psychotic individuals with ASD report more experiences of social defeat:

- More loneliness (UCLA Loneliness Scale)
- More reports of being ostracized (OES-A)
- Greater severity of bullying experienced before age 17 (Bullying Questionnaire)

- Greater discrepancy between the need to belong to others (Need to Belong Scale) and the perceived availability of informal support (ISEL)

(i.e. relatively lower perceived availability of support compared to their need to belong)

- Smaller social network (LSNS)

2c) In patients with ASD, measures of social defeat correlate highest with [18F]DOPA influx (Ki) value in the associative subdivision of the striatum (and less with similar values in the whole striatum and limbic and sensorimotor subdivisions).

2d) The greatest difference in [18F]DOPA influx (Ki) value between patients with ASD and healthy controls will be found in the associative subdivision of the striatum (this difference will be smaller in the whole striatum and limbic and sensorimotor subdivisions).

2e) Striatal [18F]DOPA influx values correlate with the number of sub-clinical psychotic experiences (PQ-16).

Onderzoeksopzet

- Testing day 1.

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On the first testing day, participants will be screened for in- and exclusion criteria.

1. Written informed consent

2. General questions (handedness; urbanicity; contact details GP; subtype and date of ASD diagnosis) and general screening on in- and exclusion criteria

3. ADOS-2 (patients only)

4. CIDI (the general practictioner (GP) of the participant will be contacted after the test session to verify medication use)

- 5. FIGS
- 6. DART
- 7. CAARMS
- Questionnaires at home:
- 8. BDI-II
- 9. STAI-t
- 10. ADHD Rating Scale-IV
- 11. AQ
- 12. CTQ
- Testing day 2 (preferably within 4 weeks of testing day 1).
- 13. Screening for metal objects in/around the body
- 14. MRI scan

- Testing day 3 (preferably within 6 weeks of testing day 1).

On the third testing day, participants complete questionnaires measuring (approximates of) social defeat and socioeconomic status. Additionally, the PET/CT scan will be made.

- 15. OES-A
- 16. UCLA Loneliness Scale
- 17. Need to Belong scale
- 18. ISEL
- 19. PQ-16
- 20. Bullying questionnaire
- 21. LSNS
- 22. BSMSS
- 23. Urine drug/pregnancy test
- 24. PET/CT scan

Onderzoeksproduct en/of interventie

Procedures for ASD patients (n=45) and healthy controls (n=24) are the same, except for the first testing day, on which patients with ASD additionally complete the ADOS-2. All participants (ASD patients and healthy controls) will be assessed on four separate occasions:

- 1. Screening for in- and exclusion criteria.
- 2. Questionnaires at home.
- 3. Anatomical MRI to delineate relevant subdivisions of the striatum.

4. PET/CT-scan to image [18F]DOPA uptake in the striatum. One hour before imaging, participants consume carbidopa (150mg, tablet) and entacapone (400mg, tablet), to reduce the formation of radiolabeled [18F]DOPA metabolites. Before the PET-scan, a low dose CT scan (120 kVp, 35 mAs) will be acquired of the brain for attenuation correction purposes of the PET images. After the CT scan, [18F]DOPA (150 MBq) will be administered intravenously, followed by a 90-minute dynamic PET scan.

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- 1. Patients: DSM-5 diagnosis of Autism Spectrum Disorder.
- 2. Age: 18-30 years.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Healthy controls: DSM-5 diagnosis of Autism Spectrum Disorder.

2. Autism Spectrum Disorder due to a known organic disorder (i° Syndromal ASD i^{\pm} , 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.

Exclusion criteria related to alcohol, soft/hard-drugs, medicinal drugs:

(N.B. We will not ask participants to discontinue any medication)

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.

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 (Kapur et al., 2000). 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.

Exclusion criteria directly related to MRI and PET/CT scanning:

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.

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17. Positive urine drug screen on the day of the PET/CT scan. Participants will be tested on cannabis, amphetamines, cocaine and opiates.

18. In women: lactation or positive pregnancy test on the day of the PET/CT scan.

19. Metal objects in or around the body.

Onderzoeksopzet

Opzet

Туре:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Parallel
Toewijzing:	Niet-gerandomiseerd
Controle: N.v.t. / onbekend	
Deelname	

Deelname

Nederland	
Status:	Werving gestart
(Verwachte) startdatum:	01-06-2017
Aantal proefpersonen:	69
Туре:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies	
Datum:	11-05-2017
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL6207
NTR-old	NTR6371
Ander register	ToetsingOnline: NL54244.058.15 : MEC LUMC: P15-288

Resultaten