Preschool Brain Imaging and Behaviour Project (PIP)

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Developmental disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON48368

Source
ToetsingOnline

Brief title
PIP

Condition

- Developmental disorders NEC

Synonym
autism, autism spectrum disorder (ASD); Attention Deficit Hyperactivity Disorder (ADHD); developmental delay

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Europese subsidie in het kader van Innovative Medicine Initiative (IMI) - AIMS-2-TRIALS (777394) & Horizon2020 programma van de EU (project CANDY);subsidieovereenkomst 847818

Intervention

Keyword: autism, behaviour, brain imaging, preschool

Outcome measures

Primary outcome

Primary outcome measures:

- severity of ASD symptoms, as measured by diagnostic interview (ADI-R) and observation schedules (ADOS) and by questionnaires completed by parents. The core measures are: Social Responsiveness Scale -Preschool (SRS-P), Childhood Routines Inventory-Revised (CRI-R), and Sensory Experience Questionnaire (SEQ)

Primary predictors / potential biomarkers:

1) cognitive measures (from touch screen tests) that index various aspects of executive functioning and attention (sustained attention, inhibitory control, motion-coherence, reinforcement learning), social cognition (false Belief, emotion recognition, social reinforcement learning, gaze dot probe) and sensory processing (tactile sensory processing, auditory sensory processing)
2) eye-tracking measures of social motivation (gazing at dynamic and static natural social scenes with/without language), processing of predictability (predictability contingency), and sensory processing (pupillary light reflex, multisensory integration)
3) EEG/ERP measures of face processing (in particular the N170 latency), auditory processing (habituation or auditory gamma), functional brain connectivity (social/ non-social videos and resting state), sensory processing

(tactile gating)

4) MRI measures of structural and functional brain connectivity (from

structural MRI, DTI and resting-state scan, all during sleep) and MRS spectra

of the thalamus (to measure GABA, glutamine and glutamate concentrations)

Secondary outcome

Secundary outcome measures are measures of comorbid disorders and temperament

- Early/ Childhood Behaviour Questionnaire (CBQ)

- Strength and Difficulties Questionnaire (SDQ)

- Child Sleep Habits Questionnaire

- Intolerance of uncertainty questionnaire

- High Sensitivity Child Scale

- Epilepsy questionnaire

- Diet questionnaire

Study description

Background summary

Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and Developmental Delay (DD) are highly genetic, heterogenous, neurodevelopmental disorders (NDDs) that frequently co-occur in the same individual and families. ASD is reliably diagnosed in clinical settings from around the age of 3 years. Previous studies reported distinct developmental trajectories in core symptom development (impairments in social-communication and repetitive and restricted behaviours and interests) across childhood (Lord et al., 2015, Fountain et al., 2012). In addition, approximately 40% of autistic children develop ADHD symptoms, and 20% epilepsy as they enter school. Moreover, around 40% of people with ASD have mild and 15% severe DD. Currently, language and overall intelligence level are the best predictors of long-term outcome (Howlin et al., 2008). However, beyond this, relatively little is known about the origins of individual differences in symptom development among autistic children. Hence, there is a need for prognostic biomarkers for autism.

A prognostic biomarker is a measure or test that helps clinicians to predict a child*s likely prognosis - a key concern for parents. A better understanding why a child may likely improve/ worsen in a particular area is also crucial to initiate early therapies or inform the development of new therapies.
ASD is likely also a collection of several conditions/diseases that are characterized by a common set of symptoms, as defined by the DSM-5 algorithm. The other aim of this study is to establish and validate stratification and/or outcome markers of ASD. Stratification markers allow to subtype ASD into biologically more homogeneous subgroups and to develop and test treatments according to the precision medicine paradigm.
Research into stratification, prognostic and outcome markers is ongoing in older patients with ASD (age 6 and older), and candidate biomarkers from the study in older participants will also be examined in this project in preschoolers.
This study will also investigate whether there may be shared biomarkers between NDDs (i.e. ASD, ADHD, DD), vs markers that are distinct for specific subgroups within or across categorical diagnostic boundaries.

Study objective

The main objective of this study is to identify prognostic, stratification, and/or outcome biomarkers for ASD. Prognostic marker refers to any objectively measurable test that helps to predict a child's likely developmental course; whether his or her core symptoms (in social communication, repetitive behaviours or sensory processing anomalies) become better or worse across the preschool years or whether he or she will develop co-occurring psychiatric and/ or medical conditions (e g., ADHD, epilepsy). Stratification marker refers to any test to subtype ASD into biologically more homogeneous subtypes, and outcome marker refers to any test that can be used as a proxy for later clinical improvement.

The secondary research objectives are to a) determine the link between individual variation in "typical" brain development and cognitive/ affective development over the preschool age range. b) Understand whether there may be shared biomarkers between NDDs (i.e. ASD, ADHD, DD), vs markers that are distinct for specific subgroups within or across categorical diagnostic boundaries. c) validate stratification biomarkers that are currently identified in older children, adolescents and adults with ASD in this younger age group.

Study design

The present multi-site study employs a longitudinal, multi-disciplinary design with the overarching goal to identify prognostic, stratification and/or outcome markers for ASD and related neurodevelopmental conditions. We aim to follow N=460 children (ASD=180, ADHD=50, developmental delay (DD)=50, typical development (TD)=180) from approximately 3 to 7 years. Each child will be seen

at three time-points (~3-4 years, ~4-5 years, ~5-6 years; the ADHD group will only be included in the last two time-points). Clinical core and associated symptoms will be assessed at all time-points to fit longitudinal developmental symptom trajectories. *Deep-phenotypic* measures of candidate biomarkers (including cognition, eye-tracking, EEG, and MRI acquired during natural sleep) will be assessed at the two earlier time points. This enables us to examine whether particular neurocognitive/ neurobiological abnormalities at Time 1, or the rate of change between Time 1 and Time 2, correlates with changes in symptom trajectories and/ or clinical outcome at Time 3.

Study burden and risks

This is a longitudinal project with assessments at timepoints. At timepoint 1 and 2 there is a visit to the Donders Centre (scheduled in 2 days, in total 10-12 hours). This visit at timepoint 1 and 2 involves as invasive measure a MRI scan during sleep. Other measures include psychological testing using touch screens, and eye-tracking and EEG/ERP assessments, and completion of questionnaires by the parents, online.

At time point 2, blood samples will be obtained by venapuncture.

Time point 3 involves only completion of questionnaires by the parents, online.

All procedures will be conducted by experienced and trained personnel. We will take extensive measures (see section J above) to ensure the preschooler is as comfortable as possible and to minimize discomfort and stress.

There are no specific risks associated with any of the procedures.

Potential benefits for the participants are that the study will establish biomarkers that add to the prognosis of the disorder, and/or stratify the disorder in subgroups, and/or can be used to monitor the outcome of treatments. Further, participating families will receive a brief report of the psychological and behavioural tests.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

ASD group:
- established or suspected clinical diagnosis of autism spectrum disorder according to the DSM-5 criteria
- males or females, from age 3 year onward
- non-verbal mental age >= 18 months (Mullen Scales)
- all comorbidities allowed

ADHD group:
- established clinical diagnosis of ADHD according to the DSM-5 criteria
- males or females, from age 4 year onward
- non-verbal mental age >= 18 months (Mullen Scales)
- all comorbidities allowed

DD group:
- clinical evaluation of developmental delay
- males or females, from age 3 year onward
- non-verbal mental age >= 18 months (Mullen Scales)
- all comorbidities allowed

Typically developing controls (TD):
- males and females from the age of 30 months
- no known developmental or medical condition affecting brain development and behaviour

All groups:
- Availability of a parent or caregiver who has sufficient command of language to a) provide written confirmed consent, and b) to provide information about the child*s behaviour, developmental history and symptoms.

Exclusion criteria

All groups:
- Significant hearing or visual impairments not corrected by glasses or hearing aids.
- Presence of any MRI contraindications (e.g., metal implants, braces) , failure of a parent/ legal caregiver to give informed written consent to MRI scanning, or to provide contact details for a primary care physician at centres where this is a precondition for scanning; other reasons why a particular child may not tolerate the sleep scan (claustrophobia, sensitivity to noise, 'tummy sleeper')
- MRI counterindications in the parent, or unavailability of any parent, legal guardian or otherwise familiar and trusted adult person to accompany the child to the MRI sleep scan.

ASD and ADHD groups:
- The presence of known genetic syndromes that have been associated with ASD, such as Tubereuze Sclerose, Fragiel X, Rett, Williams, etc.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-07-2020

Enrollment:	92
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	01-07-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	NL68615.091.19