The resilient brain of preterm born children

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON48425

Source
ToetsingOnline

Brief title
RESPROUT study

Condition

- Other condition
- Psychiatric and behavioural symptoms NEC

Synonym
Stress-related brain acitivity

Health condition

Hersenactiviteit na acute stress.

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Wilhelmina Kinderziekenhuis Fonds (WKZ-Fonds)

Intervention

Keyword: Brain activity, Preterm birth, Stress

Outcome measures

Primary outcome

- Brain activity measured with fMRI during emotion processing (i.e., IAPS), behavioural control (i.e., SSAT), and rest, following acute stress in premature born children compared to full-term born children.

- Factors determining variability underlying brain activity following acute stress in extremely preterm born children, such as coping strategies, life events, and personality, amongst others.

Secondary outcome

To study basal and stress-induced changes in hormonal levels (i.e., cortisol, alpha-amalyse), heart-rate, and perceived stress (i.e., VAS) in preterm born children compared to healthy controls.

Study description

Background summary

Stress leads to long-lasting and widespread alterations in brain structure and function. Due to the brain*s rapid development and its complex characteristics, it is not surprising that a preterm brain is extremely vulnerable to both exogenous and endogenous perturbations. Indeed, extremely preterm (EP) born children (<28 weeks of gestational age) continue to be at increased risk for lifelong neuropsychiatric disorders such as Autism Spectrum Disorder (ASD),

anxiety/depression, and attention-deficit/hyperactivity disorder (ADHD), with an overt expression during adolescence and young adulthood. However, whilst some develop one or more psychiatric disorders later in life, others are able to thrive after EP birth. To date, it remains unknown why some individuals show resilience in the face of stressors. We hypothesize that alterations in an individuals* stress-sensitivity might underlie these astonishing differences in outcome.

Study objective

The primary objective is twofold. First, we aim to investigate how the brain responds to acute stress and, second, which factors explain variability underlying brain activity following acute stress. The study population consists of extremely preterm born children and healthy-term born control at the age of 8-11. Our research can only be performed in children since we believe that the regulatory capacity of stressors during middle childhood is of great predictive value for several forms of psychopathology, many of which begin or intensify during adolescence.

Study design

An observational study in extremely preterm born children and healthy term-born controls at the age of 8-11. Participants will be randomly assigned to a standardized stress-condition, using the Trier Social Stress Test for Children, or a non-stress control condition. Participants will be divided into four groups: (a) healthy term-born children - non-stress condition (n=25), (b) healthy term-born children - stress condition (n=25), (c) extremely preterm born children - non-stress condition (n=25), and (d) extremely preterm born children - stress condition (n=85). The stress condition in extremely preterm born children is considerably larger as to better delineate the role of stress in the heterogeneous outcomes after preterm birth.

Intervention

Participants are randomly assigned to either a stress condition or a control condition of the Trier Social Stress Test for Children (TSST-C; Buske-Kirschbaum et al., 1997):
- healthy term-born children-non-stress (n=25)
- healthy term-born children-stress (n=25)
- preterm born children-non-stress (n=25)
- preterm born children-stress (n=85)

The TSST-C comprises three key component that has been deemed as potent psychological triggers of the HPA-axis, namely: uncontrollability, unpredictability, and social-evaluation (Dickerson & Kemeny, 2004). First, children will be asked to prepare a story, which will be judged for its quality

by a committee. The child will be told the story telling should be of better quality compared to other children of their age. After five minutes, the child is being escorted to the test room, where two committee members will be seated, as well as two fully equipped video cameras and a microphone. Children are asked to tell their story to the committee in an exciting and compelling manner while they are being videotaped. Following the speech, children will perform a mental arithmetic task, involving a serial subtraction which they have to perform as quickly and accurately as possible. The number sequence will be adapted to the child*s age, and the child is instructed to start over when an incorrect response is made. Throughout this protocol, the committee members will remain affectively neutral. At the end of the protocol, the committee will debrief the participants by saying that they were not truly judged in comparison with other children, and that they did an excellent job. The evoked moderate psychosocial stress-response is of comparable intensity to stressful situations experienced in daily life. Prior studies using the same test did no show any detrimental effects in children (e.g., Bae et al., 2015). Additionally, the TSST-C has been successfully administers without any complications in two separate studies conducted at the UMC Utrecht (METC: 08/271 and 12/224).

The control-TSST is a reliable no-stress control condition consisting of similar tasks as in the TSST-C but without the social-evaluative threat (i.e., jury, video camera), making it less stressful. The goal is to maintain a high level of research transparency, meaning that they are informed about the two experimental conditions and the aims of the study prior to task completion. The control-TSST has been successfully administered in children (see Bernhard et al., 2018).

Study burden and risks

Children and their parent(s) are invited to the UMC Utrecht for a 2* hour lasting testing day, of which ~15 minutes is spend on leisure. The current project has no direct beneficiary effects for either child or parent. Travel costs will be compensated and the child receives a small gift (i.e., ~¤2.50).

The visit includes the following tasks: (1) Informed consent procedure (~10 min), (2) MR simulator (~45 min), (3) TSST-C (~20 min), (4) one MRI scan in the 3T scanner (~60 min), and (5) collection of several saliva samples, continuous electrocardiography, subjective stress, and hair (~20 min). Total duration is 165 minutes, of which 15 minutes is spend on leisure. Prior to the visit, both child and parent(s) are asked to fill out questionnaires (see 8.3.7 for an overview). Parents will be given the opportunity to complete the questionnaires during the testing day on a computer or laptop at the department of Psychiatry (UMCU).

The risks involved in the present study are considered negligible. During the stress-induction task (Trier Social Stress Test for Children [TSST-C]), heart

rate will be non-invasively monitored. The evoked moderate psychosocial stress-response is of comparable intensity to stressful situations experienced in daily life (e.g., presenting in class). Prior studies using the same test did not show any detrimental effects in children (e.g., Bae et al., 2015). Additionally, the TSST-C has been successfully administered without any complications in two separate studies conducted at the UMC Utrecht (METC: 08/271 and 12/224).

Participants will undergo a MRI session of 60 minutes. During the MRI, children are asked to perform two tasks. The scan procedure is almost identical to the one used in the YOUth adolescent cohort (METC: 14/617). Compared to YOUth, the current study does include a different emotional processing task. The MRI scan does not require administration of any contrast agent, ionizing radiation or sedation. The MRI procedure is painless and not uncomfortable, although it does require the subject to lie still with the head and part of the body in a tunnel-like device. Children do not view the MRI experience as problematic, as shown by prior research at the UMC Utrecht (YOUth cohort, METC: 14/617). The code of conduct related to expressions of objection by minors participating in medical research, as stated by the CCMO, will be followed. Incidental findings may be noticed on the MRI scan. If medical treatment for these findings is indicated, the participants will be notified. If parents do not want to be informed about these findings, children cannot participate.

The current study aims to investigate stress-sensitivity in middle childhood, as opposed to adolescence or adulthood. Moreover, we have specifically chosen childhood as our main focus since a child*s stress-sensitivity might have persistent effects on behaviour and predisposes individuals to suffer from psychiatric disorders. In line with developmental cascades (i.e., the *spill over* or snowballing effect of one domain of competence to another domain of function), we believe that the regulatory capacity of stressors during middle childhood holds significance for the future development of several forms of psychopathology, many of which begin or intensify during adolescence (Masten & Tellegen, 2012). Hence, researching stress-sensitivity in children contributes to a greater understanding of the neurodevelopmental aetiology and functional impact of brain activity following acute stress, and will aid in providing appropriate lifelong support. It is of utmost importance to identify preterm born children with maladaptive stress-responses, to facilitate the development of early intervention and prevention programs.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Extremely preterm born children
- Gestational age <28 weeks
- Age at assessment 8-11 years., Healthy controls
- Gestational age >38 weeks
- Age and gender at assessment are matched to an extremely preterm born child included in the study.

Exclusion criteria

Extremely preterm born children
- Major chromosomal and/or congenital anomalies.
- Current psychiatric disorder (i.e., as indicated by a current DSM-V diagnosis)
- Ferromagnetic objects inside the body (see MRI screening)
- Claustrophobia
- Use of medication known to influence HPA-axis functioning (i.e., corticosteroid medication)
- Parents are not willing to provide informed consent
- Parents are not allowing unexpected findings to be reported to themselves or

their general practitioner(s)., Healthy controls
In addition to the previously mentioned exclusion criteria for preterm born children, the following criteria will disqualify prospective control participants from participating:
- Relative of the included preterm born child.
*

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	160
Type:	Actual

Ethics review

Approved WMO Date:	27-02-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	METC NedMec

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	NL67708.041.18

Study results

Date completed: 19-03-2020

Results posted: 24-10-2024

Summary results
Trial never started

First publication
24-10-2024