Antisocial developmental Trajectories

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The primary objective is to investigate brain functioning during fear conditioning and reward/punishment conditions in relation to persistent and desistent DBD patterns by means of functional magnetic resonance imaging (fMRI), in a large cohort of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Personality disorders and disturbances in behaviour
Study type	Observational non invasive

Summary

ID

NL-OMON50264

Source
ToetsingOnline

Brief title
Antisocial developmental Trajectories

Condition

- Personality disorders and disturbances in behaviour

Synonym
antisocial personality disorder - antisocial behavior

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: KNAW-AMMODO science grant (prof. dr. E.A. Crone

Intervention

Keyword: antisocial personality, neuroimaging, social brain network

Outcome measures

Primary outcome

Differential BOLD-response (i.e. blood flow to brain areas thought to reflect activation in these areas) in relevant neuronal networks during fear conditioning as well as during reward/punishment anticipation and outcome.

Amendement genetica: Genetic variation (Single Nucleotide Polymorphisms, SNPs), gene expression data.

' Amendement Wave 5': (1) Difierenttal BOLD-æsponse in relevant neuronal networks including self-concept evaluation, vicarious reward leaming and impulse control, {2) developmental changes in brain structure and (3) stability of antísocial behaviour over time.*

'EEG / Justice amendment': (addition to wave 5): EEG recording, criminal recidivism based on official registration systems [police / justice] and cyber crime.

Secondary outcome

Fear conditioning (CS-US contingency in terms of skin conductance levels, arousal and emotional valence), reward- and punishment-anticipation, self-reported criminal recidivism.

Amendement genetica:networks of functionally related genes, epigenetic

changes.

'Amendement Wave 5': behavior on affective control, social fear learing and

moral learning; self-reported criminal recidivism, testosterone.

'Amendement EEG/Justice': -

Study description

Background summary

Fear conditioning refers to the process in which a previously neutral conditioned stimulus (CS+) is associated with an aversive and fear-inducing unconditioned stimulus (US) and becomes intrinsically aversive (Pavlov 1927). According to Eysenck*s theory of antisocial behaviour development (1977), fear conditioning is an essential element of moral socialization during normal development in children. As such, impaired fear conditioning is thought to hamper moral conscience development and therefore to increase the probability of antisocial behaviour development. In line with this theory, studies in adult antisocial populations have shown poorer conditioning, relative to controls (Hare 1978, Raine 1993). To date, studies in juvenile antisocial populations, examining whether deficient fear conditioning indeed contributes to the development and persistence of antisocial behaviour at a young age have been scarce. Moreover, although new neuroimaging techniques have elucidated the brain areas and functions involved in fear conditioning in healthy populations, to date no neuroimaging studies examining fear conditioning have been performed in juvenile antisocial populations.
In addition to impaired fear conditioning, antisocial populations have been hypothesized to be characterized by higher sensitivity for reward and lower sensitivity for punishment as compared with controls (Shapiro et al 1988, Fowles 1980). While behavioural studies have started to provide evidence for these phenomena in Disruptive Behaviour Disorder (DBD) children (Matthys et al 2004), more studies are needed to reproduce these findings in juvenile delinquent populations and to identify the underlying neural mechanisms related to these characteristics, as these have not been studied to date.
To examine the relationship between the neural substrates (function of relevant brain areas, connectivity between these areas and their structure) of fear conditioning as well as reward/punishment sensitivity, and the development/persistence of juvenile antisocial behaviour, a functional

neuroimaging study is proposed. Subjects will be recruited from a unique large cohort of adolescents with a history of police contacts below the age of twelve, who have participated in three previous waves of an ongoing longitudinal project on juvenile antisocial behaviour development (Van Domburgh et al 2009). Those participants who have previously been diagnosed with early-onset DBD will be selected. These early-onset DBD juveniles will be psychiatrically reassessed for the current proposal, and subdivided in two subgroups; those who still meet the criteria for a DBD diagnosis (i.e. a persistent pattern of DBD; DBD-p) versus those who do not meet the criteria for DBD anymore (i.e. a desistent pattern of DBD; DBD-d). These subgroups will be compared with healthy controls in a neuroimaging protocol, using a fear conditioning and reward/punishment anticipation paradigm.
Furthermore, a group of juveniles from the same cohort with subclinical levels of DBD will be selected to investigate which of these children develop a persistent pattern of antisocial behaviour and which develop a desistent pattern. Including children with subclinical levels of DBD will improve the quality of dimensional (as compared to categorical) analyses and thus increase clinical relevance of this study. Furthermore, it enhances statistical power to study biosocial interactions in relation to antisocial development in this group of early-onset offenders.

We hypothesize that, first, early-onset DBD youngsters will show diminished fear conditioning, and that this phenomenon will be associated with altered function, connectivity and structure of brain areas known to be involved in fear conditioning. Second, we expect these early-onset DBD juveniles to be more sensitive to reward and less sensitive to punishment, reflected in both behavioural data and different function, connectivity and structure of reward/punishment-related brain areas. Third, we expect that the potential impairments in fear conditioning and reward/punishment sensitivity in early-onset DBD juveniles will be more pronounced in the DBD-p subgroup as compared with the DBD-d subgroup. Fourth, we expect that biosocial interactions add to the proportion of variance in antisocial behaviour explained by main effects of biological and social risk factors. Finally, we expect that proximal risk factors such as family characteristics and psychiatric co-morbidity are the most potent psychosocial predictors of deleterious late-adolescent outcomes.

In the genetic follow-up (i.e. *Amendement genetica*), the previous MRI study will be complemented by genetic research. Parallel to the emergence of new neuroimaging techniques, the field of genetics has made tremendous progress. Within the last few decades, genetics has seen groundbreaking discoveries and contemporary scholars acknowledge that many disorders and behaviors have a genetic predisposition. Several studies have demonstrated that this genetic liability is also an important contributing factor to the variance in antisocial behavior. Twin and adoption studies have shown that about half of the individual differences in antisocial behavior can be explained by genetic factors. Nevertheless, antisocial behaviour is phenotypically heterogeneous and

of polygenic nature, both of which seriously hamper current etiological investigations. The proposed research aims to tackle these two issues by using an innovative, integrated strategy incorporating genetics and imaging. By relating findings on the level of the brain with findings at the molecular level, we aim to elucidate the mechanisms underlying the antisocial development of young individuals. We seek to identify causal mechanisms responsible for antisocial development.

In the fifth wave of this study ("Amendment Wave 5") a new measurement wave is included. Central aim is to understand why not all youth with antisocial behavior with the same initial risk come to the same outcome (ie multifinality), and even if they do so, they often show different pathways ('equifinality', Odgers et al., 2008). A crucial question that remains open is unraveling the underlying mechanisms that can explain why some people persist in displaying antisocial behavior, while others do not (i.e., a declining trajectory of antisocial behavior in adolescence and adulthood). A better understanding of the mechanisms that may influence antisocial development will contribute to the development of effective prevention and intervention programs (Somma, Andershed, Borroni, Salekin & Fossati, 2018, Lee, 2018). The 12-minners cohort is now in the age of young adulthood. A period in which we can determine how these people developed. Based on the network model for social information processing by Nelson and colleagues (2016), we will investigate three mechanisms that may unravel the two different development trajectories (persistent versus desistent): self-concept, (social) reward learning and impulse control. These processes have been linked to parts of the social brain network that are sensitive to social experiences and temperament, and therefore provide a comprehensive assessment of social brain development.

Amendment 'EEG / Justice' concerns the addition of three extra measures to the Wave 5 measurement that is about to start, namely:
i) 1 additional questionnaire for cyber crime,
ii) applying for judicial / police data to map participants' recidivism via official register data (self-report antisocial behavior is already included in the original wave 5 amendment) and
iii) Adding EEG recording to the moral learning task in order to be able to link the neural correlate (temporal specific) of the moral task to the neural correlate (spatial specific) on social reward learning. In this way we gain insight into both the spatial and temporal neural correlates of social learning.

Literature references:

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Van Domburgh L, Vermeiren R, Blokland AA, Doreleijers TA. Delinquent Development in Dutch Childhood Arrestees: Developmental Trajectories, Risk Factors and Co-morbidity with Adverse Outcomes during Adolescence. J Abnorm Child Psychol 2009 37(1):93-105.

Study objective

The primary objective is to investigate brain functioning during fear conditioning and reward/punishment conditions in relation to persistent and desistent DBD patterns by means of functional magnetic resonance imaging (fMRI), in a large cohort of adolescents with a history of police contacts below the age of twelve, who have previously been diagnosed with early-onset DBD (DBD-p versus DBD-d) or had subclinical levels of DBD. Secondary objectives include investigation of connectivity between brain structures known to be involved in fear conditioning and reward and punishment through Diffusion Tensor Imaging (DTI) techniques (e.g. amygdala and ventromedial prefrontal cortex) and their structure through structural MRI.

The main objective of the genetic follow-up (*Amendement genetica*) is to test whether functional gene sets are related to putative brain endophenotypes (structure, connectivity) of antisocial behaviour in our juvenile delinquent sample. We aim to identify biological pathways underlying antisocial behaviour, which could inform and improve current treatment strategies.

The main objective of the fifth follow-up ('Amendement wave 5') is to test which underlying mechanisms can explain why some people persist in showing antisocial behavior, while others do not. Here we investigate three candidate mechanisms and their neurobiological basis: self-concept, (social) reward learning and impulse control. Secondary objectives include behavioral assessment of affective control, social learning of anxiety and moral learning.

Amendment "EEG / Justice" has the same main aim as "Amendment Wave 5". The inclusion of judicial / police data is essential to be able to classify the two groups not only by self-report but also by official registration reports. EEG recording to the moral learning task gives a unique opportunity to examine the temporal neural correlates and spatial neural correlates of the moral learning to the social reward task that is already included in Wave 5.

Study design

This study is a non-therapeutic observational cross-sectional study. It concerns the fourth wave of an ongoing longitudinal project (Van Domburgh et al 2009).

Within the genetic follow-up DNA will be collected from 250 individuals who have previously participated in our longitudinal study. The participants are informed in writing about the study and asked whether they wish to participate. Once the informed consent document has been signed, the saliva collection will take place during a home visit. During this visit, the participants provide a saliva sample using a non-invasive saliva sampling kit. Genetic analysis experiments require the genomic DNA from the study sample to be of adequate quantity and quality. Therefore, when employing saliva sampling to obtain DNA, we will encourage all study participants to provide sufficient sample (2,5 mL) to minimize potential loss of data during downstream genotyping. The spit

sample will be analyzed on a DNA microarray testing for specific single-nucleotide polymorphisms (SNPs). These SNPs represent the variation in the human genome and are further examined in a genetic association analysis in which we make use of a recently developed gene-network approach. Through this approach we expect to identify functional groups of genes that are associated with a reduced function, structure and connectivity of the brain regions that play a role in antisocial behaviour. Moreover, the obtained saliva - under the condition of funding - could be used to investigate whether certain environmental factors in childhood, such as child abuse, can bring about changes in the human epigenome. Such epigenetic design could help us to ascertain whether negative environmental factors via epigenetic modifications can lead to an increased risk of antisocial behavior. Additionally, the participants will be asked/measured on their general biometric/physiological characteristics (height, weight, skinfold, digit ratio and hip-to-waist ratio) and the MINI-International Neuropsychiatric Interview will be employed to asses the diagnosis of antisocial personality disorder (ASPD) The MINI is a brief structured diagnostic psychiatric interview for dsm-iv en icd-10 psychiatric disorders and the administration time of the antisocial personality disorder section will be approximately 5 minutes. In accordance with the diagnostic criteria for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), we will complement the short MINI interview with a small number of items to achieve full diagnostic assessment of ASPD as well as two items on smoking behavior. We will include the specifier *With Significant Callous-Unemotional Traits* to the diagnosis of Conduct Disorder that can be used in combination with the existing subtypes measured in our previous waves. This specifier consists of only 4 items and measures the presence of callous-unemotional traits. We expect that the questionnaires will take no more than 30 minutes to complete in total.

The fiffh wave(*Amendement Wave 5*) is also a non-therapeutic observational study. The fith wave is a follow-up to the fourth wave after 7-B years. This fifth
wave involves re-assessmenl of behavioral, neuropsychological and structural MRI measures from wave 4. Hcwever, the fMRI part differs from the fourth wave in that other tasks will be performed in the scanner: a self-concept task, vicarious reward leaming task and impulse control task. Next, on a behavior level, we investigate affective control, vicarious fear learning, and moral learning. In addition, we will also collect saliva samples for hormone measurements. All measurements are non-invasive

The 'EEG / Justice' amendment adds to the Wave 5 protocol a questionnaire on cyber crime, requesting justice / police data, and EEG recording (68 channel) under the moral learning task.

Van Domburgh L, Vermeiren R, Blokland AA, Doreleijers TA. Delinquent Development in Dutch Childhood Arrestees: Developmental Trajectories, Risk Factors and Co-morbidity with Adverse Outcomes during Adolescence. J Abnorm

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Study burden and risks

Non-therapeutic observational study: Although no direct benefit is to be expected for participants, this study aims at increasing insight into the mechanisms driving the pathogenesis and persistence versus desistence of early-onset DBD.

The burden of *Amendement genetica* is minimal compared to the MRI study.

The burden, benefits and risks of 'Amendement Wave 5' is comparable to the MRI study (wave 4). The MRI procedure is extended by 10 minutes (resulting in a load of 60 minutes). Participants are now young adults and are expected to be able to perform tasks during a slightly longer period of time.

'EEG / Justice amendment': For the addition to the fifth measurement, the benefits and risks will be comparable to those of the fourth / fifth measurement. EEG recording (68 channel) will now be added to the moral learning task, which takes ~40 minutes extra time.

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

Subject is in "very young offender"-cohort.
Or control subjects; subjects with the same age and educational level as participants from the "very young offender" cohort (19-25 years)

Exclusion criteria

Intraocular shreads of metal. Cardiac pacemaker, metal arterial clips, cochlear implant, implanted heart-valves, other implants or metal objects in the body (e.g. non-removable body piercings) not compatible with magnetic fields . Use of medication effecting brain functioning, except for short-acting medication that can be stopped for two days during the day of scanning and the day before. In the latter case, the physician of the participant will be consulted.
Pregnancy.

Study design

Design

Study type:	Observational non 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):	09-05-2010
Enrollment:	190
Type:	Actual

Ethics review

Approved WMO Date:	09-12-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL28844.029.09