Fear conditioning during specific conditions in antisocial adolescents: a neuroimaging study.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Psychiatric and behavioural symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON39929

Source
ToetsingOnline

Brief title
fear conditioning and fMRI in antisocial adolescents

Condition

- Psychiatric and behavioural symptoms NEC

Synonym
conduct disorder - antisocial behavior

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: adolescents, conduct disorder, fear conditioning, neuroimaging

Outcome measures

Primary outcome

Differental BOLD-response in the fear conditioning brain network during (reversal) fear conditioning and during reward/punishment sensitivity.

Secondary outcome

- Fear conditioning level (CS+ vs CS- differentiation in skin conductance level, pupil dilatation, self-reported arousal and emotional valence).

- Reward/punishment sensitivity (reaction time).

- Risk taking behavior (number of pumps in risk taking behavior task).

- Connectivity between brain structures known to be involved in fear conditioning and reward and punishment through Diffusion Tensor Imaging (DTI) techniques and resting-state fMRI (e.g. amygdala and ventromedial prefrontal cortex) and their structure through structural MRI.

Study description

Background summary

In psychiatry, youngsters displaying a pattern of persistent and severe antisocial behaviour are diagnosed with a disruptive behaviour disorder (DBD), which is the most frequently seen juvenile psychiatric disorder in general mental health clinics. In general populations the prevalence rates of DBD vary around 5%, of which about 30% develop a Antisocial Personality Disorder in adulthood. As such, it would be especially relevant to distinguish factors explaining the onset of antisocial behavior and help inform interventions to change this behavior.
One of the mechanisms hypothesized to drive antisocial behaviour development is impaired fear conditioning. 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 have shown impaired fear conditioning in adult antisocial individuals, relative to controls.
A second neurobiological mechanism that has been proposed to increase the probability of antisocial behaviour development, is dysfunctional reward / punishment sensitivity. As antisocial individuals tend to choose immediate rewarding antisocial strategies and disregard long-term negative outcomes, it has been argued that they may be more sensitive to reward and less sensitive to punishment than healthy controls. Dysfunctional reward/punishment sensitivity may lead toincreased risk taking behaviour. Moreover, not only the sensitivity to reward and punishment influences a child*s behaviour, also the flexibility to change behaviour when rewarding or punishing contingencies are changing (i.e. reversal learning) is of importance in this respect. Problems with reversal learning causes inappropriate perseveration in formerly rewarding behaviour even if this behaviour in a new condition is non-rewarding. Besides inappropriate behaviour, problems in reversal learning in children may lead to frustration and may result in reactive aggression, one manifestation of antisocial behaviour.
To date, only one study investigated fear conditioning in adolescents (age between 14 and 18 years) displaying antisocial behaviour and indeed showed impaired conditioning in this sample. Moreover, although new neuroimaging techniques have elucidated the brain areas and functions involved in fear conditioning in healthy populations and antisocial adult populations, only one study, of our own group, is using fMRI to study fear conditioning in antisocial adolescents at this moment. Furthermore, there have been no studies investigating whether disruptions in reward/punishment sensitivity and (reversal) fear conditioning are malleable to intervention. The relation between reward/punishment sensitivity and the degree of risk taking behaviour has not been studied yet (See protocol §1).
Therefore, the current study aims to investigate the effect of three experimental conditions (a basic condition, a methylphenidate condition and a placebo condition) on some of the known neurobiological mechanisms linked to the development of antisocial behaviour problems (e.g. hampered fear conditioning, higher sensitivity for reward, lower sensitivity for punishment and reversal problems) in DBD adolescents. To examine the effect of these interventions on the neural substrates (function of relevant brain areas, connectivity between these areas and their structure) of fear conditioning and reward/punishment sensitivity, a functional neuroimaging study is proposed.

In the original protocol 25 DBD patients would complete the protocol in the basic condition. However, due to slower than expected recruitment numbers of DBD adolescents and a change in the availability of the MRI scanner, in September 2014 (exact date after a positive decision of the CCMO has been given) randomisation will take place over two (placebo and methylphenidate) instead of three conditions (no-intervention, placebo and methylphenidate). Moreover, adding a reversal phase to a fear conditioning task gives the

opportunity to test two different neurobiological characteristics of antisocial behaviour in one paradigm.

The following hypotheses will be tested:
1. DBD adolescents will show diminished fear conditioning compared to HCs in the basic condition, and this phenomenon is associated with altered function, connectivity and structure of brain areas known to be involved in fear conditioning.
2. DBD adolescents will show diminished fear reversal compared to HCs in the basic condition.
3. DBD adolescents will show more sensitivity to reward and less sensitivity to punishment compared to HCs in the basic condition, and these differences are related to functional differences in brain activation patterns.
4. In DBD adolescents, fear conditioning and fear reversal will be potentiated in the methylphenidate condition compared to the placebo and basic condition.
5. In DBD adolescents, methylphenidate will increase sensitivity to punishment and decrease sensitivity to reward compared to the placebo condition and the basic condition.
6. DBD adolescents will show higher levels of risk taking behaviour compared to HCs.
7. High levels of risk taking behaviour will be correlated with increased sensitivity to reward and decreased sensitivity to punishment for DBD adolescents and HCs in the basic condition.

Study objective

The primary objective is to investigate brain functioning during (reversal) fear conditioning and reward/punishment conditions during different experimental conditions. Secondary objectives include investigation of connectivity between brain structures known to be involved in fear conditioning and reward/ punishment using Diffusion Tensor Imaging (DTI) and fMRI techniques (e.g. amygdala and ventromedial prefrontal cortex), as well as the study of structural brain differences between adolescent DBD patients and HCs using structural MRI. Additionally, this study aims to assess the relation between reward/punishment sensitivity and risk taking behaviour.

Study design

This study is a non-therapeutic experimental study in a group of subjects with a clinical diagnosis DBD and in a group of healthy control subjects. DBD subjects will be studied during specific experimental conditions. Before the MRI protocol starts, data will be collected concerning psychiatricdiagnoses, psychological functioning and social functioning. Interviews, structered and semi-structured, as well as questionnaires will be used for collecting data from the adolescent and the primary caregiver. Risk taking behaviour will be measured through a computerized task.. A total of 75 DBD patients (mean age 15

years) will be randomized over 3 different conditions (see protocol flowchart page 20). The conditions consist of a basic condition, a methylphenidate condition and a placebo condition. The healthy controls will perform the protocol in the basic condition (see protocol §5.2). In the original protocol 25 DBD patients would complete the protocol in the basic condition. However, due to slower than expected recruitment numbers of DBD adolescents and a change in the availability of the MRI scanner, in September 2014 (exact date after a positive decision of the CCMO has been given) randomisation will take place over two (placebo and methylphenidate) instead of three conditions (no-intervention, placebo and methylphenidate). Moreover, adding a reversal phase to a fear conditioning task gives the opportunity to test two different neurobiological characteristics of antisocial behaviour in one paradigm.

Intervention

one group (n=25) receives Methylphenidate (0.3-0.4mg/kg) in capsules of 5mg.
one group (n=25) receives a placebo in the same amound of capsules as the Methylphenidate group

Study burden and risks

DBD participants will be visited once at their home to be interviewed and to fill in questionnaires. This house visits will last for 2 hours . On a second appointment, the scanning session takes place (2 hours and 15 minutes).
For HCs 1 home visit will suffice for the interview and for filling in questionnaires. This may last less than 2 hours, because HCs will report less behavioral problems so the interview will last less compared to the interview of DBD adolescents. The scanning session will take 2 hours and 15 minutes.
As the only injuries reported thus far in MRI-scanners have been attributed to inadvertent presence of ferromagnetic materials or cardiac pacemakers, the risk of the magnetic fields in the MRI during proper use (which includes screening for these materials prior to scanning) is negligible according to current scientific opinion. The noise in MRI-scanners may be quite loud and could theoretically cause mild temporary hearing loss. The use of disposable earplugs has been shown to provide a sufficient decrease in acoustic noise capable of preventing this potential temporary hearing loss, while an additional head-phone is used on top of these earplugs in our protocol, further reducing the noise. Injury from MRI-procedures in our study is therefore not expected (see protocol page 9).
To minimize the burden of the scanning procedure, the maximum duration of scanning is limited to fifty minutes. Private correspondence with other researchers using MRI in children suggests that 15 year-olds generally will tolerate procedures lasting an hour. In one study, 16 adolescents (mean age 12.8) with DSM-IV diagnoses of anxiety disorders, who one would expect to be troubled easily by a fMRI procedure, all tolerated and completed a fMRI fear conditioning procedure. Furthermore, as the code of conduct concerning

non-therapeutic research in minors with MRI (as stated by the CCMO) requires, participants will be given the option to practice in a mock scanner first, reducing stress by accommodating them to the environment.
The use of a US may cause mild discomfort to the participants, due to its inherent aversive nature. The US is already used in the ongoing study of M. Cohn (ABR 28844) using predominantly the same imaging procotol as described here, with approval of the METc of the VUmc. We have investigated alternative modalities for a US and have found that an electric stimulus was the only reliable US for use in our fMRI procedure. For example, an aversive sound burst is difficult to use as US during fMRI scanning because of background noise and may cause hearing damage due to the impossibility to fine tune soundburst volume. An electric stimulus is the most commonly used US in the fear conditioning literature, and is likely to be the most valid and robust US in fMRI fear conditioning paradigms compared to other modalities. This US is usually tolerated well and does not cause any injuries. In our laboratory site there are researchers and technical crew experienced in fMRI fear conditioning paradigms and the use of associated equipment, ensuring its proper use. To minimize the burden of its use, the intensity will be individually calibrated to a *unpleasant, but painless* level (see protocol §5.2). The US will be delivered to the ankle instead of more threatening or sensitive areas. Also, the use of a partial reinforcement strategy will reduce the number of exposures to the US to seven.
After proper screening for contra indications, the risk of serious adverse events associated with the use of methylphenidate is negligible. Physical examination (blood pressure, heart rate and auscultation of the heart) will be conducted by the principal investigator, a medical doctor experienced in prescribing Methylphenidate to adolescents. Recently, large studies in children and adolescents have shown that the use of stimulants is not associated with an increased risk of cardiovascular incidents, neither during nor during the period afterwards. In addition, it is likely that many DBD participants are already familiar with Methylphenidate. Methylphenidate is a frequently prescribed medication in youngsters with ODD or CD, with our without ADHD, and is proven effective in the reduction of behavioral problems. It*s therefore very likely that participants in the proposed study already use methylphenidate, have used methylphenidate or will be advised to use methylphenidate in the near future. In general, methylphenidate use has no or only mild and transient side effects, side effects disappear after discontinuation of the treatment (approximately four hours). Studies have shown that a single dose of 0.5-0.6 mg/kg is well tolerated (see protocol page 9).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

DBD: Subject is diagnosed with ODD (oppositional defiant disorder) and/or CD (conduct disorder). The diagnosis will be confirmed by a standardized psychiatric interview (DISC). HC:IQ, SES and age similar to an adolescent in the basic condition. SES in the same category, IQ in a range of 5 points and age in a range of 1 month.

Exclusion criteria

DBD: 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 methylphenidate that can be stopped during the day of scanning and the two days before. Pervasive developmental disorder, Tourette*s syndrome, current or lifetime history of psychosis, neurologic disorder, history of head trauma, actual steroid use an IQ less than 80.
Contraindications for the use of Methylphenidate. (see protocol page 22)
HC: Standard exclusion criteria (NIH) for MRI are the presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin

or body. Contra-indications for using methylphenidate (see page 22). ODD, CD, ADHD, Pervasive developmental disorder, Tourette*s syndrome, current or lifetime history of psychosis, neurologic disorder, history of head trauma, actual steroid use an IQ less than 80. A history of serious antisocial behavior. Use of psychotropic medication

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-05-2014
Enrollment:	83
Type:	Actual

Ethics review

Approved WMO Date:	20-12-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2014
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

ID: 21639
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL39716.000.12
OMON	NL-OMON21639