Contrasting the Neural Systems of Social and Non-social Threat Regulation in the Adolescent Brain

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Anxiety disorders and symptoms
Study type	Observational non invasive

Summary

ID

NL-OMON51563

Source
ToetsingOnline

Brief title
FearLess

Condition

- Anxiety disorders and symptoms

Synonym
Extinction learning

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: Projectbeurs van de "Swedish Research Council" + "A Wallenberg Academy fellow grant from the Knut and Alice Wallenberg

Foundation"

Intervention

Keyword: Adolescents, Neuroscience, Social Safety Learning, Threat regulation

Outcome measures

Primary outcome

In each session participants will undergo a structural MRI scan and an fMRI scan whilst performing tasks. The main study parameter is the Blood Oxygen Level Dependent response (BOLD-response) in the threat regulation brain network during implicit and explicit forms of social versus non-social threat regulation.

Secondary outcome

The secondary parameters include:

- The resting-state fMRI

- Sex-steroid hormones

- Fear conditioning response

- Reactivity and regulation response

Other parameters (questionnaires for participants)

* Exit questionnaire - perception of observed learning model

* Pubertal development

* Subtests of an IQ test

* Peer influence

* General symptoms of psychopathology / anxiety / depression

* Early-life stress

* Resilience

* Sleep

Other parameters (questionnaires for parents)

* Early & current adolescent life events

* Socio-Economic Status (SES)

* Sleep

Study description

Background summary

Adolescence is a unique physical, social and cognitive transitional period from childhood to adulthood (Sisk & Foster, 2004) that involves developmental alterations on multiple levels. Adolescence constitutes a window of heightened vulnerability to psychiatric disorders (Giedd et al., 2008), such as threat and anxiety-related disorders (Kessler et al., 2005; Kim-Cohen et al., 2003; Merikangas et al., 2010). Previous research has shown that adolescents show deficits in learning about threats and safety relative to both children and adults (Drysdale et al., 2014; Ganella et al., 2018; Mclaughlin et al., 2015; Pattwell et al., 2012; Waters et al., 2017). However, our understanding of these developmental variations in threat regulation is still limited. In order to further understand the differences in threat regulation, this study will focus on three core-aspects of development: brain development, sex-steroid hormones and social sensitivity.

The general aim of this project is to understand developmental differences with respect to threat regulation, by focusing on brain development, sex-steroid hormones and social sensitivity. To achieve this, we will focus on two fundamental forms of threat regulation: implicit safety learning and explicit cognitive threat regulation. For both the implicit and explicit forms of threat regulation, we will compare the social and non-social threat regulation in the transition into an out of adolescence.

Implicit safety learning
Learning which objects or situations you should fear is critical for survival. However, it is equally important to learn which objects or situations you should not fear or not fear anymore, in light of new information, also called

implicit safety learning (i.e., fear extinction). A key feature of people with anxiety disorders is a deficit in safety learning (Graham & Milad, 2011). *Fears are educated into us, and can, if we wish, be educated out* (Karl Augustus Meninger). This is the goal of exposure therapy (ET), which is the first-line psychological treatment for anxiety disorders (Abramowitz et al., 2012). In this fear conditioning paradigm, the presentation of a neutral cue (e.g., a green light; conditioned stimulus (CS)) predicts the occurrence of an aversive event (e.g., an electric shock or loud noise, unconditioned stimulus (US)). After systematically pairing the CS and the US, the presentation of the CS alone will elicit a conditioned response (CR), which is indicative of fear. Repeated presentations of the CS in the absence of the US typically lead to a reduction in fear. This involves the formation of a safety association and can be referred to as safety learning (Vervliet et al., 2013). We will compare both the social and non-social forms of implicit threat regulation.

Explicit cognitive threat regulation
Emotion regulation allows us to adaptively respond to affective events, such as experienced threats. There are various emotion regulation strategies. The best studied strategy is cognitive threat regulation, which involves changing one*s interpretations of affective stimuli. It typically involves instructing participants to *downregulate* their emotions to feared stimuli by thinking about them in a way that makes them feel less negative (Gross, 1998). This strategy appears to be highly effective at regulating affect and physiological arousal (Buhle et al., 2014). Moreover, the core elements of cognitive threat regulation are applied in many forms of therapies that are effective in treating anxiety and threat related disorders, for instance in cognitive behavioral therapy (Beck, 2005). In this study, next to focusing on the implicit forms of safety learning, in which participants more implicitly learn which situations are safe by observing the safe experiences of others, we will focus on explicit forms of threat regulation as well. Specifically, we will focus on the cognitive regulation that taps into more effortful control processes aimed at reducing experienced threat (Buhle et al., 2014; Golkar et al., 2012). We will consider the effectivity of instructed downregulation of emotional reactions (through cognitive reappraisal, i.e. *please try to downregulate your emotions* and by social encouragements as *you can do this!*) in response to viewing threatening stimuli. We will compare both the social and non-social forms of explicit cognitive threat regulation.

Study objective

The general aim for this project would be to understand the neurodevelopmental differences with respect to implicit and explicit forms of threat regulation, by focusing on brain development, sex-steroid hormones and social sensitivity in adolescents.

The first aim would be to directly contrast the neural systems of two fundamental forms of threat regulation: (implicit) safety learning and

(explicit) cognitive threat regulation. In other words, we want to contrast the neural correlates of both implicit and explicit forms of social and non-social threat regulation in the transition into adolescence. This way, we can investigated whether differences in the neural network of either social or non-social threat regulation can successfully predict threat regulation.

The second aim would be to investigate to what extent there is a difference between young adolescents (9-12 years) and mid-adolescents (13-16 years). In line with the literature, we expect that mid-adolescents have more difficulties with safety learning than young-adolescents (Pattwell et al., 2012; Waters et al., 2017). Moreover, we want to investigate whether there is a difference in effectivity between social and non-social safety learning between both agegroups. We expect, in general, based on various researches by Golkar et al., that social safety learning is more effective than non-social safety learning for both groups. In addition, in line with the social sensitivity of mid-adolescents, we expect that for this group, social safety learning is more effective than non-social safety learning.

The third aim (exploratory) would be to investigate whether the experience of early stressful life experiences modulates the neurodevelopmental bases of implicit safety learning and explicit threat regulation. The fourth goal (exploratory) would be to investigate to what extent the experience of early-life stress influences the neural correlates of implicit and explicit forms of threat regulation.

Study design

This is a between-subject design and there is one session. This study combines the implicit and explicit forms of social and non-social threat regulation with structural and functional neuroimaging (fMRI) in related sets of experiments (described below). One group participants will undergo social threat regulation and one group participants will undergo non-social threat regulation. Saliva will be obtained from all participant to measure sex-steroid hormone levels. In addition, several questionnaires will be administered outside the scanner to assess e.g., the level of pubertal development, the experience of early-life stress and state anxiety. All of these are non-invasive measures.

Implicit safety learning
The participants first undergo a standard threat conditioning procedure in the acquisition phase in which they learn to discriminate between two stimuli (2 CS - twee neutrale gezichten) presented in counterbalanced order. The US will be a loud scream (90 dB), based on other validated threat learning paradigms in children and adolescents (Britton et al., 2013; Lau et al., 2011). In the first phase they learn to distinguish between the CS+ and the CS-. De CS+ is a neutral face that is followed by an anxious face, coupled to the US. The CS- is a neutral face that is never followed by an anxious phase and also never coupled to the US. During the safety learning phase, one group of participants

will view a pre-recorded video which shows another peer (age and gender-matched learning model) who acts very calmly when he/she is exposed to one set of the CSs (CS+) (social safety learning). The other group of participants will view the same video, but in absence of the peer (non-social safety learning). In this phase, the CS+ will not be coupled to the anxious phase / US. Lastly, participants are re-exposed to all pseudorandomized CSs, in the absence of the learning model. In this final stage, the efficacy of the safety learning can be assessed by the SCRs (MR compatible) and online ratings of subjective fear (self-reported arousal and emotional valency). The SCRs will be measured by a pair of electrodes attached to the distal phalanges of the index finger of the left hand.

Explicit cognitive threat regulation
A paradigm of social and non-social cognitive regulation will be developed inspired by previously established protocols (Buhle et al., 2014; Golkar et al., 2012; Myruski et al., 2019; Reeck et al., 2016) and will be further adapted for the use in children and adolescents (McRae et al., 2012). The procedure will exploit the influence of social support given by another individual through pre-recorded videos and contrast cognitive threat regulation in the presence of social support (social regulation group). The other participants will undergo the pre-recorded videos in absence of social support (non-social regulation trials). Neutral and negative pictures will be presented to the participant. At the start of each trial, an instruction word or video is presented in the middle of the screen (*decrease*, *look* or the pre-recorded video is shown). In response to *decrease* and the video, the participant should do try to downregulate the emotion. Then, a picture is presented (negative if instruction is *decrease* or when the video is shown), negative or neutral if instruction is to look. Thereafter, there is a self-report rating of the strength of the negative affect (scale from 1 to 4) and the self-reported success of downregulation (scale from 1 to 4). Then, the word *relax* is presented. There are four trial types: decrease negative (non-social cognitive threat regulation), look negative (non-regulation), look neutral (non-emotional), decrease negative - video (social cognitive threat regulation). The pre-recorded video is a video of a race, sex and age-matched learning model who instructs the participant to downregulate their emotional reactions (through cognitive reappraisal, i.e. *please try to downregulate your emotions* and by encouragements as *you can do this!*). This will only be shown to the participants in the social regulation group: half of the participants.
The efficacy of the cognitive threat regulation can be assessed by the SCRs (MR compatible) and online ratings of subjective fear (self-reported arousal and negative affect). The SCRs will be measured by a pair of electrodes attached to the distal phalanges of the index finger of
the left hand. Pictures stimuli will be taken from the International Affective Picture System (Lang et al., 1997). Several other researchers, for instance McRae et al. (2012) and used these pictures as well, in children and in adolescents and adults (Stephanou et al., 2016). In line with, McRae et al. (2012) we will remove the *worst* pictures, to make sure that these are

suitable for all ages.

Study burden and risks

No known risks are associated with the participation in the proposed measurements. MRI scanning is a non-invasive technique without catheterizations or introduction of exogenous traces. Many children and adults have undergone MRI studies without any apparent harmful consequences, as long as the absolute contra-indications are adhered. Absolute contra-indications include the presence of intra-cranial or intraocular metal or a pacemaker. A relative contra-indication is claustrophobia. Some people might experience claustrophobia while inside the scanner. If this happens during the study, it will be terminated immediately at the subject's request.

Nevertheless, we are aware that participating in an fMRI study might be a challenge for children. However, we consulted with other research groups and they were able to successfully conduct similar procedures in children. Based on that, we argue that the research plan is feasible. Moreover, the tasks are not performance-based, i.e. participants are encouraged to do their best but they will not be evaluated on their performances.

Although the participants do not receive direct benefits from participation, there are greater benefits for society from the knowledge that could be gained from the proposed research. This knowledge is needed to better understand the neural systems involved in threat regulation in adolescents. We focus on the broad range of adolescent years because of the fact that there is a large increase in prevalence of anxiety disorders in (early) adolescence. We are convinced of the need to take a developmental approach to study social and non-social threat regulation in adolescence. Specifically, given that our understanding of these developmental variations in threat regulation is still limited. Moreover, if it appears that adolescents show a greater reduction in fear in response to social threat regulation compared to non-social threat regulation, or to the implicit instead of the explicit form of threat regulation, this could be adopted in future therapies.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Fluent Dutch speaker
- 9-16 years old
- Right-handed

Exclusion criteria

- Participants with current use of psychotropic medications (unless they quit 24 hours before participation) or oral contraceptives
- (Possible) pregnancy in females
- Current and/or past psychiatric conditions
- Current and/or past neuroendocrine conditions
- Current and/or past epilepsy or head trauma
- Contraindications for MRI, including: metal implants (including braces), heart arrhythmia and claustrophobia.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-08-2023
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO

Date:	04-11-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL80802.058.22