[A novel mechanism-based treatment for pediatric anxiety disorders]

Principal Investigator:

Chad Sylvester, M.D., Ph.D.

Version Date/Number:

2 – 12/10/2020

A Introduction

A1 Study Abstract

Anxiety disorders are the most common form of pediatric psychiatric illness, affecting up to 30% of youth by age 18.[1] These disorders often produce marked impairment,[2] are associated with aberrant neurodevelopment,[3] and predict high risk for various forms of adult psychopathology.[4] While successful early intervention can occasionally interrupt this cascade,[5,6] most affected children remain symptomatic even with the best available treatments.[7] This study tests a novel, safe, mechanism-based treatment for pediatric anxiety disorders: a computer-delivered cognitive training program designed to rehabilitate the brain's ventral attention network (VAN). 90 children between the ages of 7 and 17 years of age will be enrolled at 2 sites (45 at Washington University and 45 at the NIMH). Children will be randomly assigned to active versus placebo cognitive training. Clinical symptoms and brain activity (measured with functional magnetic resonance imaging: fMRI) will be measured before and after training. This study has the potential to provide a novel, safe treatment for anxiety disorders as well as uncover the neural associates of this treatment.

A2 Primary Hypothesis

The active cognitive training program decreases symptoms of anxiety in children with anxiety disorders relative to sham training.

A3 Purpose of the Study Protocol

This study protocol is to be used as the working document for the study team to ensure that the conduct of the research is consistent with what has been approved by the IRB.

B Background

B1 Prior Literature and Studies

Anxiety disorders are the most common form of pediatric psychiatric illness, affecting up to 30% of youth by age 18.[1] These disorders often produce marked impairment,[2] are associated with aberrant neurodevelopment,[3] and predict high risk for various forms of adult psychopathology.[4] While successful early intervention can occasionally interrupt this cascade,[5,6] most affected children remain symptomatic even with the best available treatments.[7] Recent advances in neuroscience elucidate potential brain-based targets for novel therapies, which may improve this outlook by providing advances over current therapies.[3] This study tests a novel, safe, mechanism-based treatment for pediatric anxiety disorders: a computer-delivered cognitive training program designed to rehabilitate the brain's ventral attention network (VAN). This study has the potential to lead to a novel treatment with a known mechanism of action, which targets a major public health problem.

Treatments targeting the VAN may reduce anxiety by reducing neural activity associated with the involuntary capture of attention by salient stimuli. Prior research links anxiety disorders to an overactive ventral attention network (VAN),[8] which encompasses the ventrolateral prefrontal cortex (VLPFC) and temporal-parietal junction (TPJ) and supports involuntary capture of attention by salient stimuli.[9] Infants at risk for anxiety disorders exhibit signs of an overactive VAN, including increased attention and increased VAN activity in response to novel stimuli, such as new toys and people.[10-12] Moreover, in brain imaging studies, the investigators have linked abnormally increased VAN reactivity to anxiety in older children, adolescents, and young adults.[13-18] Importantly, related disorders such as major depression and ADHD are not associated with an overactive VAN, suggesting specificity to anxiety.[8,19] Taken together, this set of findings supports the hypothesis of an overactive VAN in pediatric anxiety disorders and suggests that reducing VAN reactivity may have a specific effect in reducing anxiety symptoms. Yet, no treatments have been developed to explicitly correct VAN dysfunction by directly targeting this network. The treatment tested in this study aims to fill that gap.

Computer-based cognitive training programs provide a safe, tolerable tool to reduce VAN reactivity and potentially treat pediatric anxiety disorders. Randomized controlled trials already support the use of cognitive training programs with targets different from the VAN.[20-22] For example, attention bias modification (ABM) trains individuals to ignore threatening stimuli in order to improve symptoms of anxiety.[23] While promising, this treatment generates no more than modest effects on symptoms.[24,25] The treatment in this study was specifically designed to reduce reactivity of the overactive VAN associated with pediatric anxiety disorders, by training individuals to actively ignore salient stimuli while maintaining attention on a particular task. By targeting a particular brain network that implements a core psychological process disrupted early in the developmental pathway to anxiety disorders, this novel treatment could represent a major improvement to current cognitive training approaches and may have a more substantial impact on symptoms.

B2 Rationale for this Study

Previous findings support the hypothesis of an overactive VAN in pediatric anxiety disorders and suggest that reducing VAN reactivity may have a specific effect in reducing anxiety symptoms. Yet, no treatments have been developed to explicitly correct VAN dysfunction by directly targeting this network. The treatment studied in this project aims to fill that gap. The rationale of this research is that it could lead to a novel, safe, mechanism-based treatment for a major public health problem.

C Study Objectives

C1 Primary Aim

Test the efficacy of a novel computer-based cognitive training program in the treatment of pediatric anxiety disorders using a pilot double-blind, randomized, placebo-controlled

design. The primary outcome will be reduction in symptoms of anxiety as measured by the Pediatric Rating Scale (PARS).

C2 Secondary Aim

Uncover the neural effects of the cognitive training program using functional magnetic resonance imaging (fMRI).

C3 Rationale for the Selection of Outcome Measures

The PARS is a clinician-administered measure of pediatric anxiety that incorporates both parent and child report.[26] Because it includes multiple informants and is anchored by a clinician, it has high reliability and validity and is widely used.

D Investigational Agent

D1 Preclinical Data

This is the first study to use this exact computer training regimen for testing in its ability to reduce symptoms of anxiety in children with anxiety disorders. Each session of the computer game takes approximately 30 minutes and subjects complete 8 total sessions over one month. The computer game involves paying attention to parts of the screen while distracting square boxes appear at other locations. A target “X” appears at the location that participants are paying attention to and the subjects press a button when it appears. We have piloted this protocol in 4 healthy children between the ages of 7 and 17 years of age. The procedure was well tolerated with no adverse events reported in any of the subjects.

D2 Clinical Data to Date

There are no clinical data to date on this computer training program. Other cognitive training programs such as attention bias modification that involve similar procedures have proven effective for treating anxiety disorders in meta-analyses with no known adverse events reported.

D3 Dose Rationale and Risk/Benefits

The dose is based on dosing of computer-based cognitive training programs in the literature. We will have subjects complete between 250 and 300 trials of the training program (30 minutes total) for each session; subjects complete 8 total training sessions.

Potential benefits are reduced anxiety and improved attentional control.

There are no known significant risks to this treatment. Potential mild risks include boredom, fatigue, and slight stiffness from sitting in a chair for 30 minutes.

E Study Design

E1 Overview or Design Summary

The study consists of a Baseline Psychiatric Assessment, Baseline Neuroimaging Assessment, Cognitive Training, Follow-up Psychiatric Assessment, and Follow-up Neuroimaging Assessment.

Baseline Psychiatric Assessment: Subjects and their primary caregiver undergo a psychiatric interview (regarding the child) and answer questions regarding recent symptoms. Children also complete 3 different computer games (taking between 60 and 90 minutes total). These computer games are designed to measure stimulus-driven attention, attention bias to threat, and attentional control.

Baseline Neuroimaging Assessment: Subjects undergo fMRI while they perform a task that measures their stimulus-driven attention and attention bias to threat.

Cognitive Training: Subjects are randomly assigned to either active or sham training. Subjects are blinded to assignment. Both groups complete 8 total sessions of training over one month; each session take approximately 30 minutes.

Follow-up Assessment: Subjects complete follow-up Psychiatric and Neuroimaging Assessments. These assessments are identical to the corresponding Baseline Assessments and are designed to assess behavioral and neural response to training.

E2 ***Due to COVID-19, participants may be contacted via phone and e-mail to participate in some follow-up surveys. Once contacted, we may set up a zoom meeting. A member of the research team will explain that this is completely optional and will review the online survey process with the family over the phone or zoom. If the family agrees to participate, the research team member will e-mail a RedCap survey link that will start with the consent form. Researcher will walk participant through how to complete the surveys over the phone or zoom. Participants will have adequate time to review the consent document and there will be an e-mail address provided if the participant should have any questions. The participants e-signature through REdCap will have a time stamp. After the consent is signed, research staff will send an electronic copy of the signed consent document to the participant via e-mail.*** *Subject Selection and Withdrawal*

Subjects will be screened over the phone standardized parent-report psychiatric instruments (Screen for Anxiety and Related Disorders, SCARED; and Mood and Feelings Questionnaire, MFQ).

2.a Inclusion Criteria

We will recruit children between the ages of 7-17 for this study with current separation anxiety disorder, generalized anxiety disorder, and/or social phobia.

2.a Exclusion Criteria

Exclusion criteria include prior diagnoses of ADHD, autism spectrum disorder, intellectual disability (IQ<70), a significant medical problem, or current use of psychotropic medication other than SSRIs (children who are currently taking an SSRI and are still experiencing symptoms of anxiety will not be exluded).

2.b Ethical Considerations

There are no major ethical concerns associated with this study.

2.c Subject Recruitment Plans and Consent Process

Children will be recruited through local schools, pediatricians' offices, and through Dr. Sylvester's child anxiety clinic by asking staff to present IRB approved recruitment materials to potentially interested families. We will also recruit with advertisements, press releases, websites, and placement of approved flyers and materials throughout the greater Washington University community as well as throughout the St. Louis community.

A member of the research team will review screening materials and contact potential participants by phone. This member of the research team will provide parent participants with information about the study and required elements of consent over the telephone prior to obtaining the parent's verbal consent to participate in the screening elements of the study (Initial Phone Screen as well as SCARED/MFQ). After obtaining verbal consent, a research assistant will administer the Initial Phone/Exclusion Screen to all potential participants. If a parent and child meet eligibility criteria for enrollment in the study based on their Initial Phone Screen, and parents indicate they wish to continue with the study, the research team will arrange an in-person assessment. On the day of the in-person assessment, a research assistant will provide ample time for the parents to read/review the consent form and will answer any questions the parent may have prior to signing.

2.d Randomization Method and Blinding

Subjects will be randomized to active vs. sham treatment on a 50/50 basis. The participants and the staff performing the pre- and post- treatment psychiatric interviews will remain blinded throughout the study. Study staff administering the treatment will be aware of the active vs. sham status of the participant, in order to deliver and monitor the appropriate cognitive training program.

2.e Risks and Benefits

There are minimal risks associated with this study. Parents and children may feel uncomfortable or bored during the first assessment during the clinical interview. There is also a risk of breach or confidentiality. During the cognitive training, risks for child participants include boredom and very slight physical discomfort due to sitting and using a chin rest. MRI scans involve no major risks for subjects without implanted metal objects. Subjects are extensively screened before scanning and are not allowed to participate if they have any implanted metal objects. Additional minor potential risks of MRI are discomfort from being in a small space and lying still in one position for a long time. There are also loud noises made by the scanner but subjects will wear earphones to mask the sound.

The benefits to this study are that the treatment could potentially alleviate symptoms and distress in a participant. Also the participant is receiving a free diagnostic assessment, which typically is expensive and takes a long period of time to get an appointment.

2.f Early Withdrawal of Subjects

Subject participation in the study is completely voluntary and they can choose to withdraw at any time.

2.g When and How to Withdraw Subjects

If subjects meet exclusion criteria in their initial in office assessment, they will be withdrawn from the study. Subjects may also choose to withdraw from the study at anytime.

E3 Study Device

Cognitive Behavioral Training

3.a Description

The cognitive training program is designed by Dr. Sylvester. It is designed to lower activity in the VAN by reducing the influence of extraneous, salient stimuli, thereby reducing stimulus-driven attention and potentially anxiety.

To begin a trial, subjects fixate a central crosshair; 150 ms later, an arrow “cue” appears at the center of the screen and subjects are instructed to voluntarily direct their attention toward the location indicated by arrow. Following a random delay of 1, 2, or 3 seconds, subjects indicate whether a “target” (that always appears at the location indicated by the initial arrow cue).

Active training: In between the presentation of the cue and target, three “distractor” boxes appear at irrelevant locations at random times. Subjects are instructed to ignore these boxes. It is the active ignoring of these boxes, while maintaining attention voluntarily at the cued location that is proposed to reduce subjects’ stimulus-driven attention and reduce excessive VAN activity. **Sham training:** Subjects perform the same

number of trials, of the same task, with the exception that the “distractor” boxes never appear. Thus, subjects still have to voluntarily direct attention, but they do not get practice ignoring irrelevant distractors. Both subjects and clinical interviewers will be blinded to active versus sham treatment. Subjects will be randomized to treatment arm.

3.b Treatment Regimen

Half of the subjects will be randomized to active cognitive training and half will be randomized to sham training. Children will participate in 8 total 30-minute training sessions, twice a week for 4 weeks.

3.c Method for Assigning Subjects to Treatment Groups

Subjects will be randomized to active vs. sham treatment on a 50/50 basis.

3.d Subject Compliance Monitoring

Subjects will be participating in the cognitive training program twice a week for four weeks in the presence of a trained research assistant.

3.e Blinding of Study Drug

Subjects will not be aware if they are participating in the active or sham treatment.

F Study Procedures

F1 Screening for Eligibility

Subjects will be screened over the phone standardized parent-report psychiatric instruments (Screen for Anxiety and Related Disorders, SCARED; and Mood and Feelings Questionnaire, MFQ).

F2 Visit 1

Child/Parent In-Office Assessment:

Parents will begin by completing Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Edition (K-SADS-PL), the Pediatric Rating Scale, (PARS), and the Family Interview for Genetic Studies (FIGS) with trained research staff. These semi-structured interviews will be audio taped and will only be listened to by study staff. Parents will also complete additional questionnaires. The child will participate in a computer game that is designed to test various aspects of their attention.

The child will rest their chin on a chin rest and their eye movements will be recorded. There are three different versions of the game. In each version, the computer game involves looking at a central “+” sign and pressing a button when a target appears in

either the center of the screen or the periphery. The child will also view different shapes and faces (happy, sad, angry, scared, and neutral) while engaged in the computer game. Following the game, the child will answer questionnaires (general questionnaire, SCARED, Childhood Depression Inventory (CDI), MFQ, and Pubertal Development Scale(PDS)) and participate in the child version of the K-SADS and PARS.

F3 Visit 2

Neuroimaging Visit:

MRI Simulation/Stillness Training: Child participants will complete a MRI training session to collect data on movement inhibition and prepare subjects for future MRI testing. Research indicates that an MRI simulation exercise prior to scanning increases the likelihood of a successful scan. Given that, an introduction to/explanation of the scanning procedure and a simulation exercise will be introduced at the conclusion of the child assessment. The child interviewer will engage the child in an MRI simulation. In this simulation, the child will practice lying still in a mock scanner environment. The child will practice lying still while listening to recorded MRI sounds and receiving visual feedback of their head movement. Feedback will be provided using motion tracking software, MoTrak 3D, connected to a video screen viewed from the scanner by the research subject. Subject movement and responsiveness to the training procedures will be recorded. Children will also be shown a video in which the scanning center is introduced and the scanning procedure is explained to the child. In the video, the child will see another child participating in the MRI procedure.

The NEUROIMAGING TRAINING could take place on the same day following the IN-PERSON ASSESSMENT, on the same day before the NEUROIMAGING VISIT, or on its own day, depending on the preference of the participant.

Before the MRI scan, parents will complete the MRI Safety checklist to ensure the child safety in the scanner and the child will complete a shortened version. The child will complete a 90 minute MRI scan before and after the cognitive training. We acquire a T1-weighted MP-RAGE, a T2 image, 4 five-minute “resting” functional scans, and 4 four-minute “task” functional scans. During the resting scans, the subjects with fixate a cross and during task blocks, subjects will complete the attention tasks. There will be no contrast used for this MRI scan.

F4 Visit 3-10

The child will participate in 8 thirty minute training sessions, twice a week for four weeks. They will complete the cognitive training program that has been designed by Dr. Sylvester.

On the day of sessions 2, 4, 6, and 8 subjects and parents complete the SCARED either in office or by a secure e-mail survey invitation via REDcap in order to assess anxiety over treatment. After session 8, subjects will be asked to rate tolerability of the training on a 5 point Likert scale.

F5 Visit 11

This visit will be after all 8 training sessions are completed and is identical to visit 1.

F6 Visit 12

This visit will be after all 8 training sessions and visit 11 are completed and is identical to visit 2.

Follow-up via Phone/Zoom

A member of the research team will explain that this is completely optional and will review the online survey process with the family over the phone or zoom. If the family agrees to participate, the research team member will e-mail a RedCap survey link that will start with the consent form. Researcher will walk participant through how to complete the surveys over the phone or zoom. Participants will have adequate time to review the consent document and there will be an e-mail address provided if the participant should have any questions. The participants e-signature through REdCap will have a time stamp. After the consent is signed, research staff will send an electronic copy of the signed consent document to the participant via e-mail.

G Statistical Plan

G1 Sample Size Determination and Power

Power analyses for two-tailed, two independent groups (active versus sham) comparisons were performed using G*Power 3.1. Based on prior work, we expect training to have a minimum effect size of 0.3 for changing symptoms of anxiety. Based on this effect size, we have 83% power to detect group differences in treatment effects (n=90, plus 10% failure). Power calculations are not computed for fMRI analyses because we have no effect size estimate; sample size is similar to other recent pilot studies.

G2 Interim Monitoring and Early Stopping

Subjects may withdraw from the study at any time. Each cognitive training session takes place in the lab. Study staff will converse with study subjects before and after each training session in order to assess for any adverse events.

G3 Analysis Plan / Statistical Methods

The primary outcome will be reduction in symptoms of anxiety as measured by the SCARED in study Phase 2. Total SCARED scores at sessions 2, 4, 6, and 8 will be subtracted from the baseline SCARED score, yielding a delta SCARED score for each

visit. These data will be analyzed with a mixed random effects repeated-measures model. In this model, time, treatment (active versus sham), and time x treatment interaction are fixed effects; baseline SCARED scores and subject within treatment are random effects; and delta SCARED scores are the dependent variable. Our hypothesis predicts a significant time x treatment interaction, with a greater decrease in anxiety from pre- to post- training in the active relative to the sham group. Secondary outcomes will include symptoms of anxiety on the PARS and diagnostic status.

We will test whether active versus sham training significantly reduces symptoms in children with anxiety disorders. The primary outcome will be reduction in symptoms of anxiety as measured by the PARS. We will perform a 2 x 2 ANOVA with treatment arm (active versus sham) and time (pre- versus post-training) as effects of interest.

G4 Missing Outcome Data

We will use an intention-to-treat analysis and carry the last observation forward. Because this is a pilot study, we will also compare active versus sham treatment among completers in a follow-up analysis.

G5 Unblinding Procedures

The principal investigator will be made aware of each subject's assignment after that subject has completed all study procedures including post-treatment psychiatric assessment.

H Data Handling and Record Keeping

H1 Confidentiality and Security

Telephone conversations about the study, the consent process, and all portions of the study will take place in a private office. All subjects will be marked with a random identification number so names will not be recorded on any of the data. All data will be stored in locked filing cabinets and on password protected computers. Also, only the research team will have access to study information. Participants can refuse to answer any questions and withdraw from the study at any time.

H2 Training

All current study staff have extensive experience in study procedures, based on similar prior studies performed in the lab. Any new personnel will be trained by current study staff.

H3 Case Report Forms and Source Documents

All data will be labeled with a number and not the participant's name. All electronic data will be stored in a locked cabinet and on password protected and encrypted data storage devices/computers. Paper/hard copy records will be stored in a locked filing cabinet in a locked room.

H4 Records Retention

All data will be retained and destroyed once the study is completed.

I Study Administration

I1 Organization and Participating Centers

National Institutes of Mental Health, Bethesda, Maryland & Washington University School of Medicine, St. Louis, MO

I2 Funding Source and Conflicts of Interest

Institutional Grant/Award: FBJH/ICTS
Federal Agency: NIH, National Institute of Health
ATTENTION AND RELATED FUNCTIONAL BRAIN NETWORKS IN PEDIATRIC ANXIETY DISORDERS

There are no conflicts of interest.

I3 Subject Stipends or Payments

Caregivers and child will be paid a total of $25 an hour together for each in person assessment, $50 for the completion of the cognitive training, and an additional $25 per hour for neuroimaging sessions.

Caregivers and child will be paid a total of $50 for completion of the follow-up surveys on a Forte Card.

I4 Study Timetable

Our goal is to randomize 90 subjects to active versus sham treatment over 18 months at two sites (Washington University and the National Institute of Mental Health). To achieve, this goal we will recruit, on average, 2.5 subjects per month per site. The current plan is to perform this study from January 2018 through June 2019.

J Publication Plan

Manuscripts reporting the primary outcome of the study as well as the neural effects of training will be written at the completion of the study.

K Attachments

K1 Informed consent documents

Novel Treatment Study Assent
Novel Treatment Study Imaging Assent
Novel Treatment Study Imaging Consent
Novel Treatment Study Informed Consent
Novel Treatment Consent for Phone Screen

K2 Questionnaires or surveys

Screen for Anxiety Related Disorders (SCARED)
Mood and Feelings Questionnaires (MFQ)
Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version(K-SADS-PL)
Childhood Depression Inventory (CDI)
Attention General Questionnaire
Contact Information Sheet
Pediatric Anxiety Rating Scale (PARS)
Pubertal Development Scale (PDS)
Family Interview for Genetic Studies (FIGS)
Conners

L References

1 Kessler, R. C. *et al.* Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593-602, doi:10.1001/archpsyc.62.6.593 (2005).

2 Woodward, L. J. & Fergusson, D. M. Life course outcomes of young people with anxiety disorders in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry* **40**, 1086-1093, doi:10.1097/00004583-200109000-00018 (2001).

3 Pine, D. S. Research review: A neuroscience framework for pediatric anxiety disorders. *Journal of child psychology and psychiatry, and allied disciplines* **48**, 631-648, doi:10.1111/j.1469-7610.2007.01751.x (2007).

4 Mian, N. D., Wainwright, L., Briggs-Gowan, M. J. & Carter, A. S. An ecological risk model for early childhood anxiety: the importance of early child symptoms and temperament. *J Abnorm Child Psychol* **39**, 501-512, doi:10.1007/s10802-010-9476-0 (2011).

5 Ginsburg, G. S. *et al.* Naturalistic Follow-up of Youths Treated for Pediatric Anxiety Disorders. *JAMA Psychiatry* **71**, 310, doi:10.1001/jamapsychiatry.2013.4186 (2014).

6 Benjamin, C. L., Harrison, J. P., Settipani, C. A., Brodman, D. M. & Kendall, P. C. Anxiety and related outcomes in young adults 7 to 19 years after receiving treatment for child anxiety. *Journal of Consulting and Clinical Psychology* **81**, 865-876, doi:10.1037/a0033048 (2013).
7 Piacentini, J. *et al.* 24- and 36-Week Outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS). *Journal of the American Academy of Child and Adolescent Psychiatry* **53**, 297-310, doi:10.1016/j.jaac.2013.11.010 (2014).
8 Sylvester, C. M. *et al.* Functional network dysfunction in anxiety and anxiety disorders. *Trends Neurosci* **35**, 527-535, doi:10.1016/j.tins.2012.04.012 (2012).
9 Corbetta, M., Patel, G. & Shulman, G. L. The reorienting system of the human brain: from environment to theory of mind. *Neuron* **58**, 306-324, doi:10.1016/j.neuron.2008.04.017 (2008).
10 Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E. & Ghera, M. M. Behavioral inhibition: linking biology and behavior within a developmental framework. *Annu Rev Psychol* **56**, 235-262, doi:10.1146/annurev.psych.55.090902.141532 (2005).
11 Fox, N. A. *et al.* Frontal activation asymmetry and social competence at four years of age. *Child Dev* **66**, 1770-1784 (1995).
12 Kagan, J., Reznick, J. S., Snidman, N., Gibbons, J. & Johnson, M. O. Childhood derivatives of inhibition and lack of inhibition to the unfamiliar. *Child Dev* **59**, 1580-1589 (1988).
13 Sylvester, C. M. *et al.* Resting state functional connectivity of the ventral attention network in children with a history of depression or anxiety. *J Am Acad Child Adolesc Psychiatry* **52**, 1326-1336 e1325, doi:10.1016/j.jaac.2013.10.001 (2013).
14 Sylvester, C. M., Hudziak, J. J., Gaffrey, M. S., Barch, D. M. & Luby, J. L. Stimulus-Driven Attention, Threat Bias, and Sad Bias in Youth with a History of an Anxiety Disorder or Depression. *J Abnorm Child Psychol* **44**, 219-231, doi:10.1007/s10802-015-9988-8 (2016).
15 Sylvester, C. M. *et al.* Early Childhood Behavioral Inhibition Predicts Cortical Thickness in Adulthood. *J Am Acad Child Adolesc Psychiatry* **55**, 122-129 e121, doi:10.1016/j.jaac.2015.11.007 (2016).
16 Guyer, A. E. *et al.* Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Archives of general psychiatry* **65**, 1303-1312, doi:10.1001/archpsyc.65.11.1303 (2008).
17 Monk, C. S. *et al.* Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *The American journal of psychiatry* **163**, 1091-1097, doi:10.1176/appi.ajp.163.6.1091 (2006).
18 Monk, C. S. *et al.* Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Archives of general psychiatry* **65**, 568-576, doi:10.1001/archpsyc.65.5.568 (2008).
19 Huang-Pollock, C. L. & Nigg, J. T. Searching for the attention deficit in attention deficit hyperactivity disorder: the case of visuospatial orienting. *Clinical Psychology Review* **23**, 801-830 (2003).
20 Eldar, S. *et al.* Attention bias modification treatment for pediatric anxiety disorders: a randomized controlled trial. *The American journal of psychiatry* **169**, 213-220 (2012).
21 Shechner, T. *et al.* Attention bias modification treatment augmenting effects on cognitive behavioral therapy in children with anxiety: randomized controlled trial.

J Am Acad Child Adolesc Psychiatry **53**, 61-71, doi:10.1016/j.jaac.2013.09.016 (2014).
22 Lowther, H. & Newman, E. Attention bias modification (ABM) as a treatment for child and adolescent anxiety: a systematic review. *J Affect Disord* **168**, 125-135, doi:10.1016/j.jad.2014.06.051 (2014).
23 Bar-Haim, Y. Research review: Attention bias modification (ABM): a novel treatment for anxiety disorders. *Journal of child psychology and psychiatry, and allied disciplines* **51**, 859-870, doi:10.1111/j.1469-7610.2010.02251.x (2010).
24 Hakamata, Y. *et al.* Attention Bias Modification Treatment: A Meta-Analysis Toward the Establishment of Novel Treatment for Anxiety. *Biological psychiatry*, doi:10.1016/j.biopsych.2010.07.021 (2010).
25 Beard, C., Sawyer, A. T. & Hofmann, S. G. Efficacy of attention bias modification using threat and appetitive stimuli: a meta-analytic review. *Behavior therapy* **43**, 724-740, doi:10.1016/j.beth.2012.01.002 (2012).
26 The Pediatric Anxiety Rating Scale (PARS): development and psychometric properties. *J Am Acad Child Adolesc Psychiatry* **41**, 1061-1069 (2002).