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Normalization of the auditory startle reflex after symptom reduction in children with anxiety disorders

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ABSTRACT

Background: In an earlier study the Auditory Startle Response (ASR) of anxiety disordered (AD) children proved to be enlarged. This study examines in a controlled design to what extent this increase is responsive to symptom reduction during Cognitive Behavioral Therapy (CBT)
Methods: The activity of 6 muscles following 104 dB tones in 20 patients ($M = 12,7$ years; $SD = 2.5$) and 25 matched controls was measured with an electromyogram (EMG). In addition, the sympathetic skin response was investigated. Response to treatment was investigated with the Anxiety Disorder Interview Schedule for Children (ADIS-C) and the Spence Children's Anxiety Scale (SCAS).
Results: Treatment responders ($n = 12$) showed a significant ASR decrease over time, whereas non-responders ($n = 8$) showed a significant ASR increase or no significant ASR difference. In controls, the ASR was not significantly different at follow up compared to baseline. The sympathetic skin response was stable in controls and treatment responders but significantly increased over time in treatment non-responders. Linear regression suggested that one of the ASR pre-treatment parameters (multiple muscle EMG magnitude) predicts treatment response.
Conclusions: The ASR decreases in AD children when anxiety symptoms diminish. In addition, the ASR may be useful in predicting response to CBT in AD children.

1. Background and objectives

It has been proposed that children and adolescents with anxiety disorders (AD) show abnormal fear responses while perceiving, evaluating, and responding to emotional stimuli (Pine, 2007), and knowledge about the neurobiological underpinnings of these abnormalities is accumulating (Bakker et al., 2009a; Granger et al., 1994; Boyce et al., 2001; Thomas et al., 2001; Guyer et al., 2008). It is not clear, however, to what extent parameters are responsive to change in symptom severity, for instance through treatment (McClure et al., 2007). A better understanding of this relationship is important, because if pre-treatment neurobiological abnormalities disappear with treatment, they may ultimately prove to be useful as treatment evaluators in children and adolescents with anxiety disorders (McClure et al., 2007).

The aim of the present study is to provide novel insights into neurobiological mechanisms accompanying a reduction of anxiety in AD-children by studying the Auditory Startle Reflex (ASR) before and after 12 weeks of CBT. The ASR is one of the fastest responses of the fear system and often used to assess physiological hyper responsiveness in clinical studies (Bakker et al., 2006). In two studies of adult populations the ASR has been used as a neurobiological parameter of treatment success (Karl et al., 2004), respectively as a predictor of treatment response (Merckelbach et al., 1995). Karl et al. (2004) investigated seventeen survivors of motor vehicle accidents who were treated for a posttraumatic disorder (PTSD) with CBT. Posttreatment the startle response (measured over the orbicularis oculi muscle only) was significantly reduced. The authors hypothesized that this reflected enhanced orbitofrontal cortical control over limbic networks including the amygdala. Merckelbach et al. (1995) investigated twenty women with spider phobia before and after behavioral treatment. The startle response was measured (over the orbicularis oculi muscle only) before treatment. This measurement was used to predict treatment success (evaluated behaviorally), but was not repeated after treatment. The pre-treatment magnitude of the ASR showed

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a negative correlation with treatment success immediately and at nine months after treatment. The authors hypothesized that the ASR indexes the subjects' disposition to avoid threatening stimuli. To our knowledge the ASR has not yet been employed in the investigation of treatment success, or the prediction thereof, in children. We believe this is an important line of research, because psychophysiological measures, such as the ASR, may provide a more objective index of treatment success than self- or parent-report (Karl et al., 2004).

In a previous study we were the first to demonstrate that the ASR, when measured over multiple muscles, as well as the sympathetic skin response, is augmented in AD-children (Bakker et al., 2009a). This increase was absent when measurement of the ASR was restricted to the auditory blink response alone. This corroborated earlier findings showing that the ASR measured over multiple muscles provides different results than the ASR based upon recording orbicularis oculi muscle activity alone (Bakker et al., 2009b, 2010). In the present study we re-examined the ASR parameters in patients 12 weeks after starting cognitive behavioral therapy (CBT), in which a minimum of 10 sessions had been offered. The second time point of the study did not necessarily coincide with the end of treatment. Rather than measuring the effect of treatment, we assessed response to the first 10–12 sessions. Similarly, we re-examined controls after a similar period of time. The following questions were addressed: 1) Is the ASR still abnormal in patients compared to controls after a significant improvement during treatment? We hypothesized a decrease of the ASR in patients when clinically improved. 2) Is there a difference in ASR change for the treatment responders, treatment non-responders and controls? We hypothesized that the ASR parameters would decrease in all subjects (in controls due to a test-retest effect) but that the effect would be most pronounced in patients who had responded to treatment, similar to the study of Karl et al. (2004). 3) To what extent does ASR magnitude predict treatment success? Due to the exploratory nature of this question, no hypothesis was formulated. 4) To what extent are the findings regarding the first three research questions dependent of the way the ASR is measured (multiple muscles versus the auditory blink response only)? We hypothesized that the EMG multiple muscle findings would correlate best with the clinical findings.

2. Materials and methods

2.1. Participants

We approached all patients referred to the outpatient clinic of the Academic Center for Child and Adolescent Psychiatry de Bascule in Amsterdam between August and November 2006 that met inclusion criteria for the study. Inclusion criteria for participation were: 1) at least one principal AD diagnosis; 2) age between 8 and 17 years. Patients were excluded from the study if they took medication, had a hearing defect, or met criteria for one or more of the following disorders: major depression disorder, neurological disorder, mental retardation or schizophrenia or other psychotic disorders. Of the 25 AD patients included in the study we could not follow up 5 patients of which all suffered primarily from a social anxiety disorders (1 started taking medication, 3 refused to return and 1 did not return calls/letters). This left a total of 20 anxiety disorder patients for analysis. We included the baseline and follow up measurements of only these 20 patients in the analysis. The patients often suffered from multiple anxiety disorders, with the following principal anxiety disorders: social anxiety disorder (nine), generalized anxiety disorder (eight), specific phobia (two) and panic disorder (one). Comorbidity included dysthymia (six) and attention-deficit disorder in remission (one). We invited controls on the basis of similarity of age and sex to the clinical group, preferably from the circle of friends or acquaintances of the patient, and we excluded them if they met criteria for psychopathology, took medication, had a hearing defect or suffered from a neurological disorder. This led to 25 controls matched to the original 25 anxiety disorder patients. Most controls were indeed friends or acquaintances of the patients; four subjects were acquaintances of the researcher. Education level of all subjects was established. We assessed all subjects at baseline and at follow up. All subjects were non-smokers. A more extensive description of the study group is provided elsewhere (Bakker et al., 2009a).

2.2. Treatment

All patients received weekly individual CBT. The CBT was a 12-session Dutch adaptation of the Coping Cat program (Kendall et al., 1990; Nauta et al., 2001) provided by certified CBT therapists during the 12 weeks between baseline and follow up measurements at the outpatient clinic. Patients received at least 10 sessions.

2.3. Procedure

Patients and controls were seen twice: at baseline and at follow up 12 weeks later. The follow up took place after 12 weeks irrespective of the stage of treatment (the follow up session did not mark the end of the treatment). One of us (MJB) interviewed patients and their parents at baseline and at follow up with a semi-structured psychiatric interview (see below). Controls and their parents were interviewed only at baseline. We administered anxiety symptoms questionnaires (see below) both at baseline and at follow up to patients, parents of patients, controls and parents of controls. The two ASR testing sessions (baseline and follow up) were identical. We assessed the ASR PM, usually in the late afternoon. Informed consent of the participants was obtained after the nature of the procedures had been fully explained. We had asked the subjects to refrain from caffeinated beverages on the day of testing. After we attached the electrodes the subjects sat on a bed (with backrest) in upright position. We gave the subjects the following instructions: 'shortly you are going to hear a series of sounds. Please sit quietly and listen to the sounds as they come. Keep your eyes open throughout the entire procedure, which will last approximately 15 min. Subsequently, we placed the headphones and initiated the stimulation software. Preparation took 30 min, the experiment itself 15 min'. The study protocol and informed consent forms were reviewed and approved by the Institutional Board of the Academic Medical Center in Amsterdam. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

2.4. Psychiatric assessment

We used the Anxiety Disorders Interview Schedule for Children (ADIS-C/P) (Silverman and Albano, 1996; Nauta et al., 2004) to formally establish or exclude anxiety disorders in all subjects. The ADIS is a semi-structured interview based on DSM-IV classification of psychopathology (American Psychiatric Association, 1994) and includes both a child and a parent interview (ADIS-C C/P). Per diagnosis interference with daily functioning is judged on a scale from 0 (no interference) to 8 (high interference), with rates of 4 and higher indicating a disorder (Silverman and Albano, 1996). As recommended by the developers (see for instance Silverman et al., 2009) the ADIS-C/P was administered to each youth and mother to assess anxiety and related disorders in the child. Interviewers assigned diagnoses that youth and mother agreed were most interfering. In cases of disagreement, the interviewer considered both informants' views to derive a final diagnosis. In cases of