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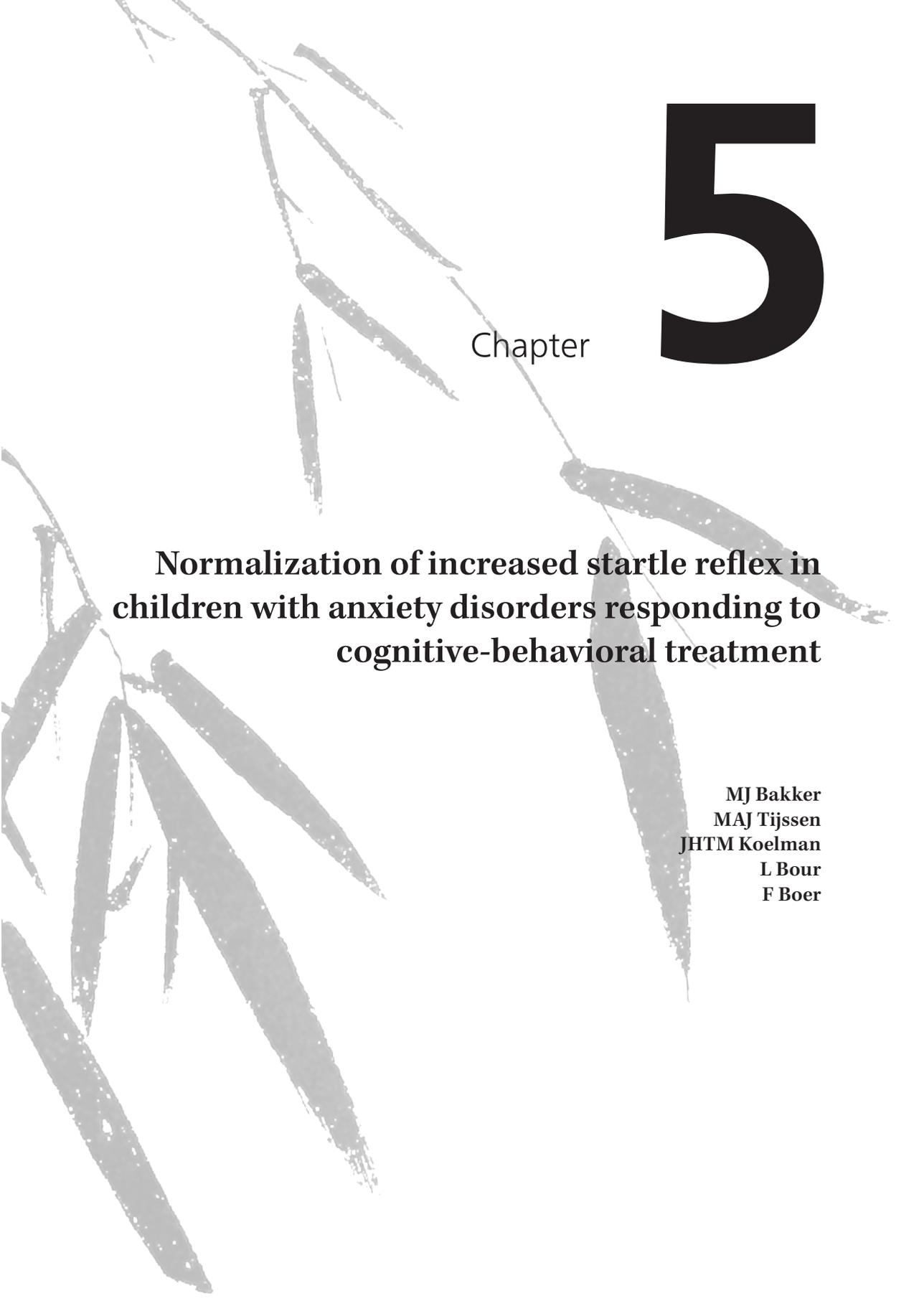
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Chapter

Normalization of increased startle reflex in children with anxiety disorders responding to cognitive-behavioral treatment

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Abstract

Objective: The Auditory Startle Reflex (ASR) measured over multiple muscles and the sympathetic skin response following auditory stimuli are increased in children with anxiety disorders compared with healthy controls, but the auditory blink response is not. In order to further study the relation of the ASR and anxiety in children, we re-examined these parameters in the same patients after 12 weeks of cognitive-behavioral therapy and in controls after a similar period of time. It was our aim to investigate the change in physiological reactivity in both patients, responders and non-responders, and controls.

Methods: We measured the activity of 6 muscles following 104 dB tones in 20 patients ($M = 12.7$ years; $SD = 2.5$) and 25 age and sex matched controls before and after treatment with an electromyogram (EMG). The sympathetic skin response was simultaneously assessed, The muscle response probability (%) and magnitude of the EMG response (area-under-the-curve in $\mu V.ms$) of the combined response of six muscles (multiple muscle ASR) and separately of the blink response were investigated. Treatment response was assessed with the Anxiety Disorder Interview Schedule.

Results: Following treatment, the multiple muscle ASR (response probability and EMG magnitude) was not significantly enlarged in patients compared with controls anymore. Treatment responders ($n=12$) showed a significant decrease in multiple muscle ASR response probability and EMG magnitude, whereas non-responders ($n=8$) showed a significant increase in multiple muscle ASR EMG magnitude. The blink response showed no significant change from pre- to post treatment. In controls, the multiple muscle ASR (response probability and EMG magnitude) was not significantly different at follow up compared with baseline but their blink response had significantly increased. The sympathetic skin response was stable in controls and treatment responders but significantly increased in treatment non-responders. Linear regression within the patient group showed that a large multiple muscle ASR EMG magnitude before treatment was predictive for a positive treatment outcome.

Conclusions: The ASRs only normalized in patients responding to treatment, suggesting that ASR decrease reflects anxiety reduction. The sympathetic skin response showed a similar pattern. In addition, the ASR may predict treatment response. These findings suggest that ultimately the ASR measured over multiple muscles may be used as treatment evaluator or predictor independent of behavioral measures. The auditory blink response does not appear to reflect anxiety changes in children.

Introduction

It has been hypothesized that children with anxiety disorders show abnormal fear responses while perceiving, evaluating, and responding to emotional stimuli.⁶ In accordance, accumulating neurobiological evidence demonstrates aberrant responses to fear stimuli in these children.^{12, 14, 22, 25} However, the effect of treatment on neurobiological stress parameters in childhood anxiety disorders has only incidentally been investigated.²⁶⁹ Such work is important, because if pre-treatment neurobiological abnormalities decrease with treatment, it might ultimately allow such measures to be used as treatment evaluators or predictors in children with anxiety disorders.²⁶⁹ In contrast, if such abnormalities remain stable they may be stronger related to the genetic vulnerability to develop pathological anxiety than to the phenotype. Cognitive-behavioral therapy is an effective treatment of anxiety disorders in children.²⁷⁰ However, some children exhibit robust treatment responses, whereas others respond more poorly. A pathophysiological heterogeneity has been hypothesized to explain these different responses to treatment.²⁷¹ Possibly this pathophysiological heterogeneity is materialized into pre-treatment neurobiological characteristics. The aim of the present study is to provide novel insights into the neurobiological mechanisms underlying the reduction of anxiety in children.

We demonstrated an increased Auditory Startle Reflex (ASR) measured over multiple muscles and sympathetic skin response in children with anxiety disorders in a previous study.²⁷² However, we could not demonstrate this increase when measurement of the ASR was restricted to the auditory blink response. In the present study we re-examined the ASR parameters in the same patients at a 12 week follow up during which cognitive-behavioral therapy had been offered in weekly sessions. Similarly, we re-examined the controls after a similar period of time. In order to further investigate the relation of the ASR and anxiety in children, we investigated the ASR changes in patients responding to treatment, patients not responding to treatment and controls. The following issues were addressed 1) Is the ASR still abnormal in patients compared with controls after treatment? We hypothesized that the ASR of the patients as a group would have normalized after treatment 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 3) Does the ASR predict treatment success? We hypothesized that the ASR, because it reflects a certain pathophysiological profile, would predict treatment response 4) What are the differences between the multiple muscle ASR and the auditory blink response in addressing issues 1, 2 and 3? We hypothesized that the blink responses would yield different results than the multiple muscle ASRs regarding these issues.

Methods

Subjects

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 primary anxiety disorder 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 anxiety disorder 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 primary anxiety disorders: social anxiety disorder (9), generalized anxiety disorder (8), specific phobia (2) and panic disorder (1). Comorbidity included dysthymia (6) and attention-deficit disorder in remission (1). We invited controls on the basis of similarity of age and sex to the clinical group, 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. We assessed all subjects at baseline and at follow up. All subjects were non-smokers. See²⁵⁰ for a more extensive description of the study group.

Treatment

All patients received weekly individual cognitive-behavioral therapy from certified cognitive-behavioral therapists during the 12 weeks between baseline and follow up measurements at the outpatient clinic. Patients received at least 10 sessions. The sessions were not protocolized but individually fitted cognitive-behavioral interventions.

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) to both patients, their parents, controls and their parents at both baseline and follow up.

The two ASR testing sessions (baseline and follow up) were identical. We assessed the ASR PM, usually in the late afternoon. 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 minutes'. Subsequently, we placed the headphones and started the stimulation software. Preparation took 30 minutes, the experiment itself 15 minutes. The study protocol and consent forms were reviewed and approved by the Institutional Board of the Academic Medical Center, Amsterdam.

Psychiatric assessment

We used the Anxiety Disorders Interview Schedule (ADIS)^{255, 256} to formally establish or exclude anxiety disorders in all subjects. The ADIS is a semi-structured interview based on DSM-IV classification of psychopathology³⁶ and includes both a child and a parent interview (ADISC/P). One of us (MJB; clinical psychologist) gave a final clinician's impairment score for each anxiety disorder on the basis of the impairment scores regarding this anxiety disorder of both the child and their parents.²⁵⁵ After treatment, we classified all patients as "treatment responder" or "treatment non-responder". A positive treatment outcome (treatment responder) was defined as a reduction in impairment on the ADIS of at least two points. We classified the patients into treatment responder or treatment non-responder before analysis of the startle data. In addition, another investigator who was blind for the startle data (FB; child psychiatrist) confirmed all treatment outcome decisions independently on the basis of the child and adult version of the ADIS. This was particularly important in cases in which impairment scores of children and their parents did not automatically lead to a clear outcome decision, e.g. when the ADIS-scores were very different in parents or children or many diagnoses were present with different changes in impairment scores. In addition, we sought confirmation by investigating change-scores on an anxiety symptoms questionnaire, the Spence Children's Anxiety Scale (SCAS)^{256, 273, 274} which includes both child and parent reports. To be considered a treatment responder, scores on the SCAS-child and SCAS-parent together should show a reduction of least 20 points. This second criterion confirmed the classifications. All patients considered treatment responders showed this SCAS-reduction, whereas the SCAS-score changes of the patients considered non-responders showed a reduction under 20 points, no change or an increase.

ASR assessment

Experimental stimuli consisted of 8 consecutive 104 dB (A) (sound-pressure level), 50 ms, 2000 Hz pure tones with instantaneous rise and fall times.⁶⁵ We presented the tones with varying time intervals (1.5 – 2.5 minutes)^{58, 90}, similar for all subjects, binaurally through stereo headphones. An audio-stimulator generated the tones following a digital trigger. We recorded physiological data, consisting of bipolar left orbicularis oculi, masseter, sternocleidomastoid, deltoid, abductor pollicis brevis, quadriceps electromyography (EMG) and sympathetic skin response measures employing Biosemi's Active System (www.biosemi.nl). We recorded the sympathetic skin response from the palm of the hands, with the reference electrode on the dorsum of the hands.^{219, 228} See²⁵⁰ for details regarding data collection. After skin preparation, we filled the cutaneous silver-silver chloride flat active surface electrodes with conductive paste and attached them 2 cm apart with adhesive collars.⁶⁵ We checked the impedance of the electrodes (<10 k Ω) before start of the ASR assessment. The signal was analogue filtered high-pass (1st order; -3dB at 0.16 Hz) and low-pass (5th order anti-aliasing; -3dB at 3500 Hz). Filtered data were continuously digitized with a sample frequency of 16384 Hz per channel using a 24-bit A/D converter. Details of the data processing have been described elsewhere.²⁵⁰ After the test one of us (MJB) visually inspected the EMG activity of all muscles to determine the response probability of each muscle. We scored a 'response' if an increase of EMG activity from baseline occurred in either of the six simultaneously recorded muscles at an appropriate latency.^{45, 47, 89} We used the following rules defined before analysing the data: (1) a response is a clear increase (duration increase at least 30 ms, magnitude response at least 30 μ V) from baseline (2) the response onset (20-200 ms following stimulation) is marked at the baseline (thus at the start of the μ V increase) (3) all responses are scored by the same investigator (MJB) (4) all responses are scored at the same screen sensitivity (200 μ V on the screen, 100 μ V below baseline and 100 μ V above baseline). We determined the response probability of the individual muscles by counting the total occurrence of muscle responses and dividing this value by the total amount of recorded traces (8), and multiplying this value by 100. We defined the multiple muscle ASR response probability as the average of the response probabilities of the six muscles.⁵⁸ Latency was defined as the period between stimulus onset and the start of the response at the EMG baseline. Response onset (latencies) and response offset were manually marked by the investigator. We marked trials considered artefacts (e.g. heart beat, loose electrodes) as such and excluded these from the analysis. We defined the multiple muscle ASR magnitude of the EMG signal as the summated log transformed EMG area-under-the-curve of the individual muscles⁵⁸, with the area-under-the-curve as quantifier (expressed in μ V.ms) of the EMG signal between response onset and offset, based on the responses scored by the investigator.⁵⁸ In a previous study we showed

that the magnitude of the EMG based on responses scored by the investigator was not influenced by investigator's bias.²⁷² We defined the sympathetic skin response as the difference in μV between the identified maximum (the peak μV during the interval 900 - 4000 ms following stimulation) and the baseline (mean μV during 0-900 ms following stimulation) standardized to (relative to; giving values ranging from 0 to 100 %) the intra-individual maximum.^{235, 236}

Visual Analogue Scale

We collected the subjective report of the startle reflex intensity at the end of the startle session using a Visual Analogue Scale (VAS), specifically a Facial Affective Scale²⁷⁵ with 5 emotional faces ranging from "not startled at all" (face 1, happy face) to "very much startled" (face 5, crying face).^{275, 276} The subject marked his/her perceived startle reactivity on a line with a pencil. The score (0 – 4) to which the mark was closest was considered his/her final score. Therefore, the VAS was a Likert scale with the values 0 ('not startled at all'), 1 ('startled a little bit'), 2 ('startled'), 3 ('startled considerably') and 4 ('startled very much').

Statistical analysis

Statistical analysis was performed with SPSS (15.0). We used a linear mixed-model analysis (type III tests of fixed effects) to test the effect of group (patients versus controls) on the repeatedly elicited responses (8 trials) before treatment and after treatment. We used the same test to investigate the effect of measurement (follow up versus baseline) on the repeatedly elicited responses (8 trials) for each group. The analyses were conducted under the assumption of compound symmetry for the covariance structure which is equivalent to the classical approach to repeated measures ANOVA. A linear regression analysis was used to relate the repeatedly elicited responses at baseline to treatment outcome (treatment responders versus non-responder). One-way ANOVA's were used to test general characteristics and paired sample T-tests were used to test the difference in anxiety symptoms at follow up compared with baseline. The EMG area-under-the-curve's were log transformed to reduce skewness. We did not analyze the Visual Analogue Scale statistically. A p-value ≤ 0.05 was considered significant in all tests.

Results

Group characteristics

20 anxiety disorder patients (7 boys; $M = 12.9$ years, $SD = 2.6$) and 25 controls (10 boys; $M = 12.0$ years, $SD = 2.5$), all measured at baseline and follow up, did not differ significantly

in sex ($F(1)=0.64$, $p=0.265$) and age ($F(1)=1.9$, $p=0.163$). At follow up the anxiety symptoms of the patients as assessed by both SCAS-child report ($T(20)=2.8$, $p=0.011$) and SCAS-parent report ($T(20)=4.8$, $p=0.000$) were significantly reduced compared with baseline. In the controls there was no significant reduction of anxiety symptoms as reported by the children (SCAS-child $T(20)=1.7$, $p=0.098$) and their parents (SCAS-parent $T(25)=1.6$, $p=0.118$).

Treatment outcome

Of the 20 anxiety disorder patients, 12 patients (3 boys) were classified as treatment responders and 8 patients (4 boys) as treatment non-responders. These groups did not significantly differ in sex ($F(1)=2.6$, $p=0.110$), age ($F(1)=0.6$, $p=0.802$) or anxiety symptoms before treatment (SCAS-child $F(1)=0.186$, $p=0.672$); (SCAS-parent $F(1)=0.328$, $p=0.574$), indicating that the severity of anxiety symptoms before treatment was not related to treatment outcome.

At follow up the anxiety symptoms of the responders as assessed by both SCAS-child report ($T(12)=4.2$, $p=0.001$) and SCAS-parent report ($T(12)=3.4$, $p=0.006$) were significantly reduced. In non-responders the anxiety symptoms were not significantly different at follow up compared with baseline as assessed by SCAS-parent report ($T(8)=0.333$, $p=0.749$) but SCAS-child report did show a significant decrease, ($T(8)=3.5$, $p=0.008$).

Physiological responsiveness before treatment

Before treatment anxiety disorder patients and controls differed significantly in multiple muscle ASR response probability ($F(1, 42)= 5.1$, $p=0.029$), multiple muscle ASR EMG magnitude ($F(1, 42.2)=7.1$, $p=0.010$) and sympathetic skin response ($F(1,40.9)=5.1$, $p=0.029$) with patients showing a higher responsiveness to the tones. In contrast to the multiple muscle ASRs, the blink response EMG magnitude was not significantly different between patients and controls before treatment ($F(1,38.9)=3.4$, $p=0.071$).

Physiological responsiveness after treatment

After treatment the patients and controls did not differ significantly in multiple muscle ASR response probability ($F(1,40)=1.3$, $p=0.249$), multiple muscle ASR EMG magnitude ($F(1,41.4)=3.5$, $p=0.067$) and the sympathetic skin response ($F(1,40)=3.0$, $p=0.089$). In accordance with findings at baseline, the blink response EMG magnitude did not differ significantly different between patients and controls, ($F(1,38.9)=3.4$, $p=0.071$) at 12 week follow-up.

Change in physiological responsiveness in controls

The multiple muscle ASR response probability, multiple muscle ASR EMG magnitude and sympathetic skin response were not significantly different at follow up compared with baseline in controls, $F(1,347.8)=0.65$, $p=0.417$, $F(1,287.7)=1.2$, $p=0.264$, $F(1,354.4)=0.5$, $p=0.818$ (Figure 1 and 2). However, the blink response was significantly increased at follow up compared with baseline in controls ($F(1,273)=13.3$, $p=0.000$).

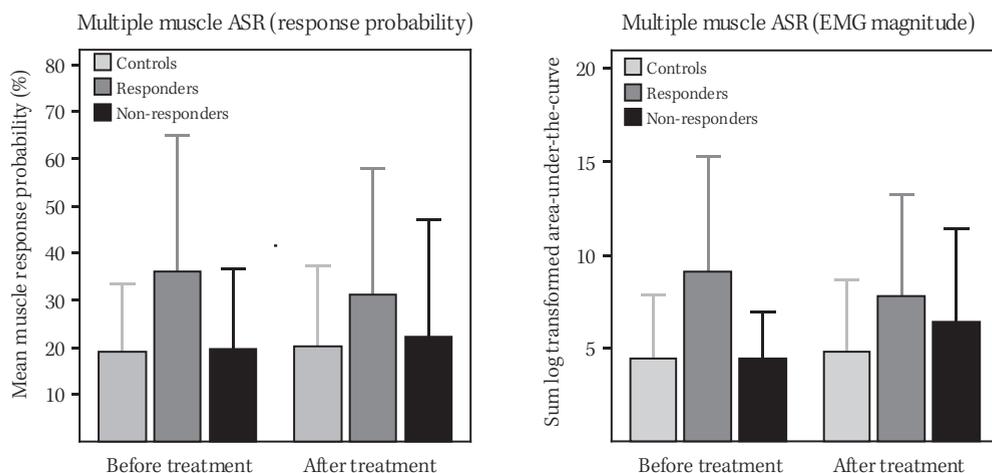


Figure 1. The multiple muscle ASR (response probability and EMG magnitude) before and after treatment in controls, treatment responding patients and treatment non-responding patients. Bars represent means, error bars standard error of means.

Change in physiological responsiveness in treatment responders

In treatment responders the multiple muscle ASR response probability ($F(1,164)=4.0$, $p=0.046$) and the multiple muscle ASR EMG magnitude ($F(1,140)=4.5$, $p=0.036$) showed a significant decrease at follow up compared with baseline (Figure 1). The blink response EMG magnitude was not different at follow up compared with baseline in the treatment responders ($F(1, 138.9)=0.11$, $p=0.731$). Similarly, the sympathetic skin response had not changed significantly following treatment ($F(1, 163)=2.5$, $p=0.116$) (Figure 2).

Change in physiological responsiveness in treatment non-responders

In treatment non-responders the multiple muscle ASR EMG magnitude ($F(1,179.7)=7.4$, $p=0.008$) and sympathetic skin response ($F(1,115.7)=4.8$, $p=0.029$) showed a significantly increased response at follow up compared with baseline (Figure 1 and 2). However, the multiple muscle ASR response probability did not significantly change ($F(1,119)=0.8$, $p=0.371$) (Figure 1A). The blink response EMG magnitude was not different at follow up compared with baseline in treatment non-responders ($F(1, 77.1)=2.8$, $p=0.094$).

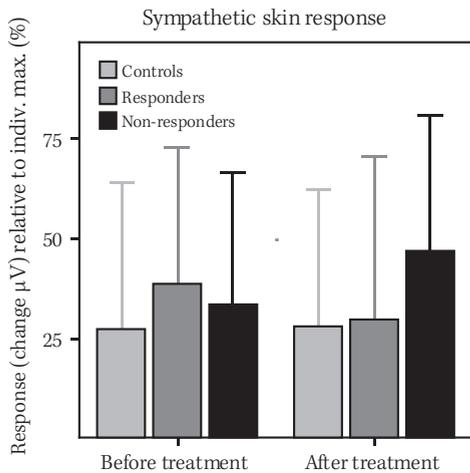


Figure 2. The autonomic sympathetic skin response following auditory stimuli before and after treatment in controls, treatment responding patients and treatment non-responding patients. Bars represent means, error bars standard error of means.

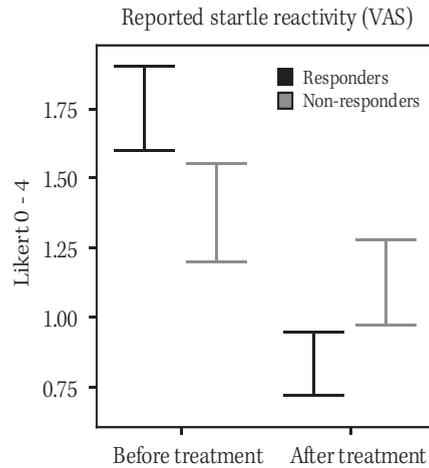


Figure 3. Visual Analogue Scale of subjective reported startle reactivity. Error bars represent standard error of means. Likert scale: 0 ('not startled at all'), 1 ('startled a little bit'), 2 ('startled'), 3 ('startled considerably*') and 4 ('startled very much').

Prediction of treatment outcome

The predictive value of physiological parameters at baseline for treatment success was investigated with a linear regression analysis, that showed multiple muscle EMG magnitude to be a significant predictor of treatment outcome ($F(1)=4.6, p=0.037$)(Figure 1B), in contrast to response probability ($F(1)=1.6, p=0.209$) blink response ($F(1)=1.3, p=0.247$) and the sympathetic skin response ($F(1,3.4), p=0.073$)(Figure 1 and 2), that did not show associations with treatment outcome.

Visual Analogue Scale

The reported startle reflex intensity as indexed by the VAS scale is shown in Figure 3.

Discussion

In the present study we demonstrated that physiological hyperresponsiveness, as indexed by the ASR measured over multiple muscles, normalizes after cognitive-behavioral treatment in children with anxiety disorders. In contrast to before treatment, the ASR was not significantly increased in children with anxiety disorders compared with controls after 12 weeks of treatment. In addition, we found a significant decrease of the ASR only in patients responding to cognitive-behavioral treatment. In contrast, the multiple muscle ASR significantly increased or remained stable in treatment non-responders. The ASR remained stable over time in healthy controls. The autonomic

sympathetic skin response following auditory stimuli showed a similar pattern: it was stable in both healthy controls and treatment responders but increased in treatment non-responders. In addition, we predicted a positive response to cognitive-behavioral therapy on the basis of the ASR before treatment.

First, these results suggest that the ASR measured over multiple muscles is associated with pathological anxiety in children, in accordance with our previous study.²⁷² Not only is the multiple muscle ASR enlarged in children with anxiety disorders, these abnormalities also normalize after the anxiety symptoms have been reduced. The stability in healthy controls of the two multiple muscle ASR parameters (response probability and EMG magnitude) and the autonomic skin response adds to the test-retest reliability and reproducibility of these measurements. The present findings therefore suggest that the ASR measured over multiple muscles may be a biological marker of the anxiety disorder phenotype in children; a tool to establish anxiety symptoms or evaluate treatment independent of behavioral measures.

It is important to emphasize that the relation between the ASR and anxiety could not be demonstrated when the assessment of the ASR was restricted to measuring the blink response. The blink response did not change significantly following treatment in the treatment responders and treatment non-responders. In fact, the blink response significantly increased in controls during the 12 weeks. These findings demonstrate that the blink response, when compared with the multiple muscle ASR, shows different results in both healthy children with children with anxiety disorders, in accordance with our previous studies^{250,272} and studies in adults with various disorders.^{47, 69, 221, 237, 249} The multiple muscle ASR pattern was more similar to that of the sympathetic skin response compared with the auditory blink response, also as in our previous studies.^{250, 272} These findings together strengthen our recommendation to investigate ASR abnormalities in (pediatric) psychiatric patients by the ASR measured over multiple muscles (the whole-body ASR).²⁵⁰

The absence of ASR abnormalities following treatment does not support the idea that an increased ASR reflects a risk factor to develop an anxiety disorder (endophenotype).^{7, 272} The findings suggest that the ASR is associated with the phenotype rather than the genotype of anxiety disorders. However, as the samples were small the exact nature of the relation between increased ASRs and pathological anxiety in children remains subject for further investigation.

Second, this study is the first to demonstrate that the multiple muscle ASR may be a predictor of treatment response. How are we to understand this finding? The pre-

treatment assessments indicate that the amount of the anxiety symptoms and the type of anxiety disorders did not differ before treatment between the patient groups. Possibly the ASR differences between the two patient groups reflect differences in their pathophysiology. In a previous study a higher pre-treatment amygdala activity was found in children with generalized anxiety disorders who were more likely to respond to cognitive-behavioral therapy and medication.²⁶⁹ The author who described this study suggested that these children suffered from anxious symptoms stemming from another neurological basis than those with lower levels of amygdala activation.²⁶⁹ In adults suffering from depression similar findings were described.²⁷⁷ Furthermore, less activity in the amygdala but more activity in the rostral anterior cingulate cortex predicted a positive treatment response to venlafaxine in adults with a generalized anxiety disorder.²⁷⁸ However, adult spider phobics who exhibited an increased fear-potentiated blink response showed a relatively poor treatment outcome and alcohol-dependent patients with increased fear-potentiated blink response were more likely to relapse.^{279, 280} As discussed, the different results described for blink response studies may be due to methodological differences.

There are limitations to this study as well that need to be addressed. The number of patients is small, especially if the patients are grouped according to treatment outcome. Further, the patients returning for the follow up measurement may be biased because of the 5 drop-outs. Finally, the cause of the change in both physiological parameters and anxiety symptoms cannot be inferred from the current findings. Due to a lack of an untreated patient control group, we cannot exclude the possibility of improvement in anxiety symptoms and ASR normalization because of effects of time or intervening events. However, it was our aim to study the relation of the anxiety symptoms with the ASR rather than the effectiveness of cognitive-behavioral therapy, already demonstrated in a number of controlled trials.²⁷⁰

Besides these limitations, we believe that this study, when replicated in larger samples, has important implications, as it suggests the possibility of identifying biological markers of severe pediatric anxiety, that are not hampered by the limitations of subjective self or parent report. It may even help us identify those children who will react well to a relatively short term cognitive-behavioral therapy, and those who will need more extensive treatment, possibly augmented with other interventions.