The startle reflex in children with neuropsychiatric disorders
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Summary
Introduction

In the current thesis we investigated the auditory startle reflex (ASR) in children with psychiatric and neurological disorders. The main focus was on children with anxiety disorders (before and after treatment) and children with functional abdominal pain. We assessed two different parameters of the ASR in these patient groups. The auditory blink response is the standard method used in psychophysiological research \(^{37, 64, 65}\), whereas a second method, measuring the response following auditory stimulation over multiple muscles (multiple muscle ASR), is the standard method in neurological ASR studies.\(^{63, 63, 251, 252}\) The purpose of the electromyographical (EMG) studies was to compare these two measurement methods and especially assess the value of the multiple muscle ASR in two prevalent childhood psychiatric disorders. In the following paragraphs the results of these studies will be summarized and discussed.

Chapter 2

We provided an overview of the literature on startle syndromes in chapter 2. We distinguished three groups of patients suffering from excessive startle reflexes or related disorders: "hyperekplexia", "neuropsychiatric startle syndromes" and "stimulus-induced disorders". The 'major' form of "hyperekplexia" (startle disease) has been described in detail. The clinical characteristics are distinctive and the pathophysiology including several genetic mutations causing the disorder are known. The etiology of the 'minor' form of hyperekplexia, excessive startle reflexes only, is largely unknown. Excessive startle reflexes can be symptomatic due to neurological damage but usually the origin is unclear and psychiatric causes are considered. Based on the literature we proposed to categorize patients as having a "neuropsychiatric startle syndrome" if additional behavioral features such as psychiatric symptoms are present. Culture-bound startle syndromes, hysterical jumpers and anxiety disorders are examples of neuropsychiatric startle syndromes. Because extensive EMG studies were not available for these syndromes this classification may change according to the yet to be investigated electromyographical characteristics. Finally, "stimulus-induced disorders" can be recognized in which startling stimuli can induce responses other than startle reflexes, such as startle-induced epilepsy. Diagnosis of startle syndromes depends on clinical history, electromyographic studies, and genetic screening.

Chapter 3

In chapter 3 the ASR was assessed in 27 healthy children. A polymyographic EMG including orbicularis oculi, masseter, sternocleidomastoid, deltoid, abductor pollicis brevis and quadriceps muscles was recorded while auditory stimuli were presented. The multiple muscle ASR was defined as the combined response probability; the mean of the
response probabilities of six different muscles, and as the combined EMG magnitude; the summated log transformed EMG area-under-the-curve of the individual muscle responses. For comparison, the blink response was defined similarly for the orbicularis oculi muscle. The habituation patterns of the multiple muscle ASR and the auditory blink response proved to be different. The multiple muscle ASR response probability showed a significant decrease over repeated stimuli. In contrast, the blink response probability did not significantly decrease over the repeated stimuli. The multiple muscle ASR combined EMG magnitude and blink response EMG magnitude both did not habituate significantly, but a decreasing trend was observed in the multiple muscle ASR EMG magnitude. The sympathetic skin response following the auditory stimuli decreased significantly over the train of stimuli, indicating that the association of the autonomic response with the multiple muscle ASR is stronger than with the blink response. Effects of gender and age on the different parameters of the ASR were not found.

It was concluded that in children the habituation of the multiple muscle ASR is more pronounced compared with the habituation of the blink response, in accordance with earlier findings in adults. As Brown found for adults, a stronger habituation of the multiple muscle ASR compared with the blink response in children suggests that it is a more valid representation of the ASR. Brown had described certain characteristics of the auditory blink response which he thought to indicate that it may not be the best tool for ASR studies; its relatively short latency, its two components and its continuing presence after repetitive stimuli. These results were confirmed in this study for children. Further, in the current study the sympathetic skin response habituated about as fast as the multiple muscle ASR supporting the idea that recording the activity of multiple muscle increases the validity of the ASR measurement. The autonomic response following the motor response is considered part of the ASR by some authors. Finally, a more extensive investigation of the ASR is appropriate because in some startle syndromes abnormalities are particularly prominent in the responses of more distal muscles.

Chapter 4
In chapter 4 we used the same methods to assess the ASR of 25 children with anxiety disorders. The primary diagnosis in most cases was social anxiety disorder or generalized anxiety disorder but they often suffered from multiple forms of anxiety disorders. The multiple muscle ASRs of these patients were significantly enlarged compared with those of 25 age and sex matched controls. In contrast, the blink response was not significantly increased in the children with anxiety disorders. The sympathetic skin response showed a comparable pattern to that of the multiple muscle ASR: it was significantly enlarged in the anxiety disorder patients. Finally, the latencies of the muscle responses did not
differ significantly between the groups. In 9 non-affected siblings the sympathetic skin response but not the multiple muscle ASR response probability was enlarged compared with controls. Effects of sex and age on the different parameters of the ASR could not be established, in accordance with the findings in healthy children.

First, the current extensive investigation supports the hypothesis that childhood anxiety disorders are associated with enlarged ASRs\textsuperscript{36, 61, 62}, in contrast to previous blink response studies and the current blink response results.\textsuperscript{33-35} The findings confirm that in children the blink response cannot be simply equated to the ASR as it occurs in the whole body, similar to adults.\textsuperscript{47} The measurement over multiple (distal) muscles gives a different, more complete representation of the ASR than the blink response alone.

Second, the findings can be considered to reflect the neurobiological correlates of a sensitive fear system in children\textsuperscript{62, 241}, concerning a direct central nervous system hyperreactivity to stressful stimuli. The ASR, measured over multiple muscles, may be a useful biological marker of pediatric anxiety, not hampered by limitations of subjectivity. As it is not under voluntary control and its measurement and quantification are straightforward, it is an attractive objective quantifier of childhood anxiety. Further, the fact that the stimuli are simple to apply and therefore easy to replicate is advantageous. Hyperarousal, hypothesized to be a distinctive feature of childhood anxiety disorders (the triparte model)\textsuperscript{357}, may explain enlarged ASRs. Abnormal Hypothalamus-Pituitary-Adrenal (HPA) axis functioning and autonomic reactivity of children with anxiety disorders have been demonstrated in previous studies.\textsuperscript{13-15, 19-28, 242, 243} As the current samples mainly exists of patients with social and generalized anxiety disorder patients, the findings may imply that hyperarousal is a general characteristic of anxiety disorders, and not only of post-traumatic stress disorder and generalized anxiety disorder.\textsuperscript{36, 358, 359}

Third, because the findings strengthen the association between enlarged multiple muscles ASRs and pathological anxiety in man\textsuperscript{37, 61, 62} it also confirms the association in humans between the ASR measured over multiple muscles and the amygdala, a key structure involved in pathological anxiety.\textsuperscript{10, 11, 62, 266} Previously, abnormal functioning of the amygdala has been associated with fear-potentiated ASRs in animals\textsuperscript{53, 244} and fear-potentiated blink responses in humans.\textsuperscript{360} Accordingly, pathological 'anxiety' (stress) has consistently been linked to an increase of the ASR\textsuperscript{315, 361-363} in animal studies, in which not the blink response but rather a whole-body ASR is assessed (whole-body jumping or the hindleg muscle response).\textsuperscript{244, 248, 361} In contrast, the association of pathological anxiety with an increased blink response in humans is less consistent.\textsuperscript{33-35, 37} The whole-body ASR in animals has been associated with the nucleus reticularis pontis caudalis
which is directly modulated by the amygdala during the stress response (see Figure 2 of the Introduction). The blink response has not been specifically related to the nucleus reticularis pontis caudalis, but is considered to be modulated by polysynaptic neural networks, although it is known to be influenced by arousal.

Most neuroscientists will acknowledge that the brain has both static and dynamic characteristics. However, researchers differ considerably in their focus, aiming at either one of these poles, or on some part along the continuum in between. It is challenging to hypothesize on whether the increased ASRs are more strongly associated with the present anxiety symptoms of the children or whether it reflects a genetic vulnerability to develop an anxiety disorder (endophenotype). The current study provides a clue with regard to whether the ASR is an endophenotype for anxiety disorders in children or not. The small group of unaffected siblings of the children with anxiety disorders also showed an exaggerated sympathetic skin response, pointing towards a relation between the reaction to sudden auditory stimuli and a vulnerability to develop anxiety. However, the group of siblings was very small (9 children). Concerning the generalizability of the findings, we feel it is likely that the enlarged ASRs of the children with anxiety disorders reflect an abnormality which also affects them in situations other than experimental settings. However, some kind of challenge like the experimental setting may be essential to reveal the ASR abnormalities.

Chapter 5

The ASR measurements were repeated after 12 weeks in both 25 healthy children and 20 children with anxiety disorders to further study the relation between the ASR and pathological anxiety in children. The results of these measurements were related to those of a psychiatric follow-up assessment after treatment. In three groups (controls, patients responding to treatment and patients not responding to treatment) the change on physiological responsiveness (ASRs and sympathetic skin response) was investigated. Results showed that the multiple muscle ASR and sympathetic skin response of the patients had normalized after 12 weeks of treatment. Similar to pretreatment findings, the blink response was not significantly different in patients compared with controls after treatment. In healthy controls the blink response had significantly increased at follow up compared with baseline but the multiple muscle ASR and sympathetic skin response had remained stable. A subgroup analysis revealed that the enlarged multiple muscle ASR had significantly decreased in patients who were successfully treated with cognitive-behavioral therapy. Their blink response had not changed significantly. In contrast, in patients who had not responded to cognitive-behavioral therapy the ASR parameters including the sympathetic skin response had significantly increased or
remained stable. Finally, a large multiple muscle ASR (EMG magnitude) before treatment was predictive for a positive treatment outcome.

Again, like in chapter 3 and 4, we demonstrated differences between the results of the auditory blink response and those of the multiple muscle ASR quantification. This supports our previous conclusion that the measurement over multiple muscles gives a different, more complete representation of the ASR than the blink response alone. Second, the results further support the association between enlarged ASRs measured over multiple muscles and pathological anxiety in children. The ASR abnormalities decreased in accordance with a reduction in anxiety symptoms. More specifically, the ASR measured over multiple muscles only significantly decreased in anxiety disorder patients who responded to cognitive-behavior therapy, not in patients who had not responded to this treatment or controls. The multiple muscle ASR may therefore be a biological marker of the anxiety disorder phenotype in children; a tool to establish anxiety symptoms or evaluate treatment independent of behavioral measures. Furthermore, because the ASR may predict treatment response in children with anxiety disorders it may help to identify those children who will react well to a relatively short term cognitive-behavioral therapy, and those who will need more extensive treatment. Finally, the fact that the ASRs were not significantly different between patients and controls after treatment appears to clash with the suggestion that increased ASRs may be an endophenotype (by definition closely related to the genotype and therefore more or less stable) of anxiety disorders in children (chapter 4). To settle this issue more research including larger samples of patients and their siblings is needed.

Chapter 6
The ASR was studied as an index for general central nervous system hypersensitivity in children with functional abdominal pain. The ASRs of 20 children with functional abdominal pain were compared with those of 23 controls and of 25 anxiety disorder patients. It was demonstrated that both the multiple muscle ASR and the blink response were increased in children with functional abdominal pain compared with controls. However, their sympathetic skin response was not significantly enlarged compared with controls. Compared with the children with anxiety disorders there were no significant differences on the ASR parameters and sympathetic skin response in the children with functional abdominal pain. No significant differences (or trends) in the ASR parameters and sympathetic skin response could be established in the patients' subgroups.

In the children with functional abdominal pain the ASR parameters yielded similar results: both the multiple muscle ASR and the auditory blink response were significantly increased in the patients compared with the controls. The results of this clinical study
demonstrate that both the auditory blink response and the multiple muscle ASR are sensitive for abnormalities present in patients in which a hypersensitivity for sensory stimuli is hypothesized. The two ASR parameters are therefore associated.

In accordance with similar findings in adults\textsuperscript{298, 302, 305-308}, this study demonstrates a hypersensitivity for non-gastrointestinal stimuli in children with functional abdominal pain. As they respond hypersensitively to auditory stimuli, it suggests children with functional abdominal pain suffer from a general hypersensitivity to sensory stimuli. In addition, their psychophysiological stress response may be similar to that in children with anxiety disorders. As in children with anxiety disorders, the results may be explained by hyperarousal. This supports the hypothesis that functional abdominal pain symptoms may be (partly) generated by determinants like hyperarousal, chronic stressors, HPA activity, sensitization etc.\textsuperscript{331}

Chapter 7

Results of multiple muscle ASR studies are reported in a child with both hereditary hyperekplexia ‘major’ form and an anxiety disorder. As mutations in the alpha1 subunit of the inhibitory glycine receptor, GLRA1, have been identified in most pedigrees with the hyperekplexia ‘major’ form, this defect may be regarded as the defining element of autosomal dominant ‘major’ hyperekplexia. Recently, mutations in other glycine-related genes have been associated with the ‘major’ hyperekplexia form. Electrophysiological and psychiatric details were studies before and during treatment with clonazepam in a SLC6A5 (GLYT2) mutation hyperekplexia case\textsuperscript{318} Our aim was to investigate whether the ASR would reduce once the hyperekplexia and related anxiety symptoms had diminished as a consequence of treatment. Before treatment, the multiple muscle ASR was dramatically enlarged compared with control subject. During treatment, both the excessive ASRs and the anxiety symptoms clearly decreased. This case report therefore confirms that clonazepam can be an effective treatment of the excessive ASR in SLC6A5 positive patients. In addition, the amount of ASR enlargement in hyperekplexia ‘major’ form is illustrated. A significant increase of the ASR could be established in children with anxiety disorders compared with controls only on a group level (chapter 4), whereas the ASR exaggeration in the present hyperekplexia ‘major’ form case is clear at an individual level.\textsuperscript{175}

Chapter 8

Children with functional abdominal pain and children with anxiety disorders are suggested to have similar psychophysiological stress responses (chapter 6). These patient groups may also show similarities in the cognitive processes associated with psychopathology. In chapter 8 the scores of administered questionnaires and clinical
interviews of children with functional abdominal pain, children with anxiety disorders and controls were compared. The study aim was to investigate the presence of cognitive abnormalities associated with the etiology of childhood anxiety disorders in children with functional abdominal pain. It was demonstrated that abnormally increased automatic anxious thoughts and anxiety sensitivity were present in children with anxiety disorders but not in children with functional abdominal pain without an anxiety disorder. Furthermore, the results showed that the presence and/or report of psychiatric and other functional symptoms is heterogeneous in children with functional abdominal pain. One subgroup suffered from a comorbid anxiety disorder and reported an increased amount of additional (non-gastrointestinal) somatization symptoms. Another subgroup was comorbidity-free, reported no additional (non-gastrointestinal) somatization symptoms and even reported a significantly lower amount of anxiety symptoms compared with controls. Anxiety symptoms, cognitive abnormalities and non-gastrointestinal somatization symptoms did not differ between children with the two Rome III diagnoses irritable bowel syndrome and functional abdominal pain syndrome.

These results suggest that automatic anxious thoughts and anxiety sensitivity are not specifically related to childhood functional abdominal pain; only to childhood functional abdominal pain combined with an anxiety disorder. The findings point to a partly non-shared etiology of childhood functional abdominal pain and anxiety disorders. That is, children with functional abdominal pain and children with anxiety disorders may be similar concerning certain stress factors (reflected in over-arousal, chronic stressors, HPA activity, sensitization etc) (discussed in chapter 6), they may differ substantially from children with anxiety disorders concerning their conscious (cognitive) experience of their stress. However, possibly the heterogeneity of the functional abdominal pain patients may have contributed to the negative findings. If children with functional abdominal pain do not suffer from an abnormal amount of negative cognitions, more specifically automatic anxious thoughts and anxiety sensitivity, this may have implications for the usefulness of cognitive-behavioral treatment in these patients.

Conclusions

The studies in the current thesis support the hypothesis that in children (both pediatric neuropsychiatric patients and controls) the ASR measured over multiple muscles is a better tool to index the ASR than the auditory blink response. However, the studied groups are small and replication studies including more patients are needed to confirm the current findings. For childhood anxiety disorders, it is especially interesting to perform future studies on the role of the multiple muscle ASR as treatment evaluator or predictor.