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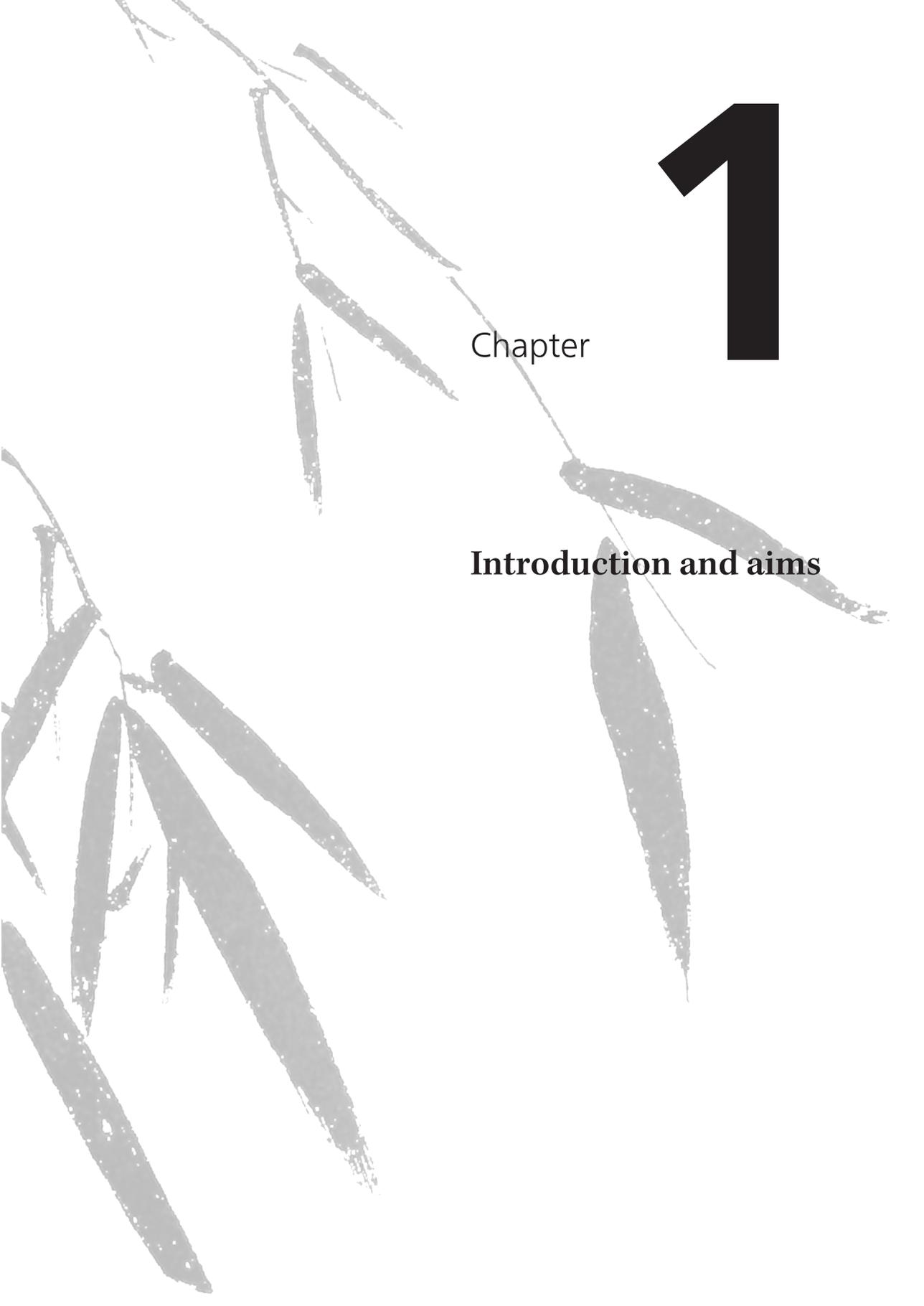
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Chapter

Introduction and aims

Anxiety disorders in children

Childhood anxiety disorders are responsible for much suffering. The prevalence of anxiety disorders in Dutch adolescents was 10.5 % ten years ago¹ but this proportion has increased in recent years.² The disorder is associated with having fewer friends, problems with peers, poor academic performance and in general a lower quality of life.³ Although anxiety disorders in children may disappear, for example following cognitive-behavioral treatment or antidepressants, they often persist for years, or recur, and therefore are considered chronic.⁴ In accordance with this apparent vulnerability a recent review described that offspring of parents with an anxiety disorder (465 children) had an anxiety disorder rate of 37%; higher than the 15% of offspring of non-anxious controls (906 children).⁵ Innate biological and environmental factors probably influence the development and persistence of the illness in a complex interaction. As a result, anxiety disorders can be described as the consequence of a genetic vulnerability combined with environmental factors.

Risk factors for anxiety disorders during adulthood include (1) childhood anxiety disorders (in particular, separation anxiety disorder and generalized anxiety disorder), (2) *behavioral inhibition* which predicts later social phobia, (3) *anxiety sensitivity* which predicts later panic disorder, and (4) *negative affect* which predicts a spectrum of psychopathology including anxiety disorders.⁵ There is also evidence pointing towards the role of parenting styles, peer influences, stressful life events and perinatal stressors.⁵ Furthermore, it has become clear that neurobiological factors are important in explaining the etiology of anxiety disorders. Deviant development of the biological systems involved in stress regulation is considered a risk factor for the development and/or maintenance of anxiety disorders.⁶ Endophenotypes such as quantitative measurements in blood or cerebrospinal fluid, data from magnetic resonance imaging, electroencephalography or electromyography are measurable risk traits presumably causally closer related to the pathogenetic phenotype than the heterogeneous clinical phenotype itself.^{7, 8} The current search for endophenotypes in psychiatry (Figure 1) attempts to improve the homogeneity of psychiatric phenotypes by studying a narrower phenotype, or endophenotype.⁸ This may also increase the chance to find molecular genetic abnormalities associated with the disorder.⁷ In addition, to date no biological parameters are available to help establish the diagnosis of anxiety disorders (biomarkers). Although there are some biological indicators described as symptoms of psychiatric disorders, these are still scarce and generally not used in clinical practice.

Both human and animal research has been helpful in delineating the neurobiology of anxiety, and in humans this network is partially localized in one of the phylogenetically

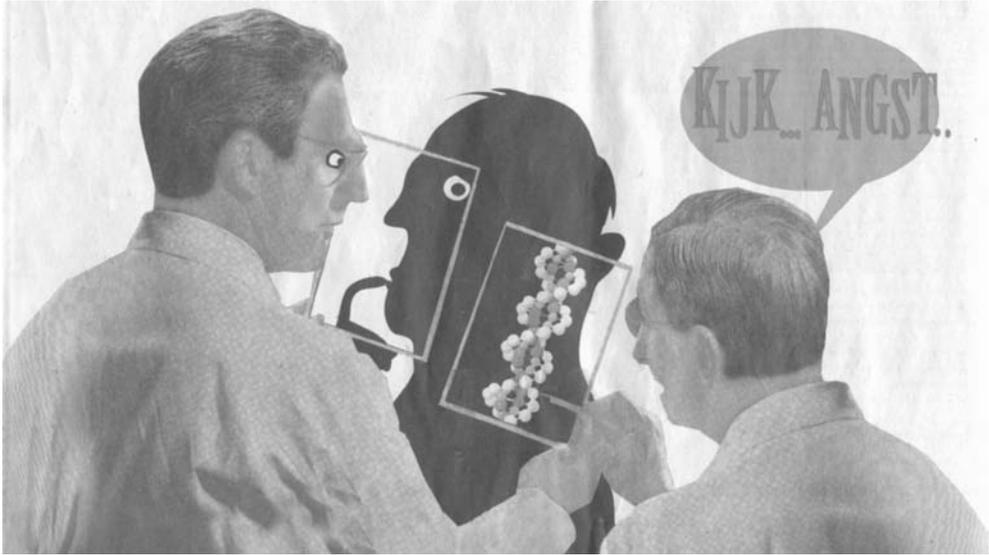


Figure 1. The search for endophenotypes in psychiatric scientific studies (Volkskrant 15 nov 2008)

oldest areas of the brain, the limbic system. The amygdala, the most important part of the limbic system, crudely compares present possibly threatening stimuli with past threatening or fear-inducing material. Subsequently, higher (phylogenetically younger) brain areas like the prefrontal cortex and the hippocampus modulate the activity of the amygdala once they have determined more precisely whether the stimuli are threatening in a given context.⁹ In anxiety disorder patients the stimuli are not truly dangerous to the individual but perceived as such. This process is considered to be mediated by a generally overactive amygdala and a weakened inhibition from the hippocampus and prefrontal cortex on the amygdala.⁹⁻¹¹ The role of the amygdala in the stress response is illustrated in Figure 2. In children with anxiety disorders amygdala hyperactivation has been demonstrated.¹²⁻¹⁶ In accordance, studies of the Hypothalamus-Pituitary-Adrenal (HPA) axis and the Autonomic Nervous System (ANS) in children with anxiety disorders in general point towards a dysfunction of these systems.¹⁸⁻²⁸ Furthermore, the immediate unconscious response when confronted with new ambiguous and/or emotional stimuli is also hypothesized to be abnormal in anxiety disorder patients.²⁹⁻³² The startle reflex, completed within 200/300 ms, is such an early parameter of the stress response. In fact, an exaggerated startle reflex is described as a symptom of posttraumatic stress disorder and of other anxiety disorders as part of the hyper-arousal criterion in the Diagnostic and Statistical Manual of mental Disorders (DSM).³⁶ However, in children research of the startle reflex has been confined to children with posttraumatic stress disorder. This research, in which only the blink response was measured, has yielded negative

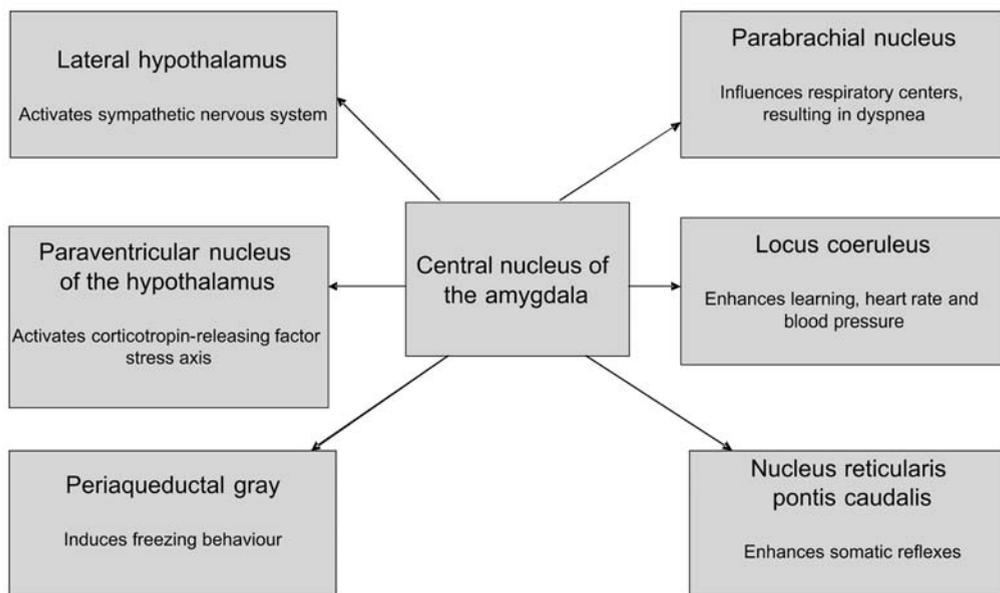


Figure 2. Role of the amygdala in the stress response¹⁷

results.³³⁻³⁵ The data supporting startle reflex abnormalities in adult anxiety disorder patients, also indexed by the blink response, are not conclusive (for a review see³⁷).

Functional abdominal pain in children

Medically unexplained somatic symptoms constitute an important reason for the referral of children and adolescents to pediatric and mental health institutions. In children, these symptoms may concern abdominal-pain related functional gastrointestinal disorders (or “functional abdominal pain”), with childhood irritable bowel syndrome and childhood functional abdominal pain syndrome as the two most common forms. Functional abdominal pain refers to chronic abdominal pain for which no organic cause can be identified; functional abdominal pain syndrome to a subcategory of the childhood abdominal-pain related functional gastrointestinal disorders according to the Rome III criteria.³⁸ The latter represents those who do not meet inclusion criteria for irritable bowel syndrome, functional dyspepsia, aerophagia or abdominal migraine. The main difference between the Rome III subcategories irritable bowel syndrome and functional abdominal pain syndrome is the absence of accompanying symptoms in children with functional abdominal pain syndrome, whereas in children with irritable bowel syndrome, pain is accompanied by changes in defecation or symptoms related to defecation. Both conditions are bothersome, affect daily life and are associated with a high medical consumption.³⁸

The pathophysiological mechanism in children with irritable bowel syndrome or functional abdominal pain syndrome is unknown. However, some hypotheses have been put forward which are partially supported by evidence. One such hypothesis concerns visceral hypersensitivity.³⁸ The term refers to an increased sensitivity of the gastrointestinal tract. It has been demonstrated that gastrointestinal stimuli which are perceived as normal, non-painful sensations in healthy persons, are interpreted as painful by patients with functional abdominal pain. However, there is no absolute proof of gastrointestinal defects and therefore a purely somatic interpretation of these findings has been questioned.³⁹ Still, there is some evidence pointing at the contribution of inflammation, prior injury or infection, and changes in the local factors of the gastrointestinal tract in functional abdominal complaints (for a review see⁴⁰). Another hypothesis was derived from the observation of a high comorbidity of psychiatric disorders in children with functional abdominal pain.⁴¹ It has been suggested that pediatric functional abdominal pain and anxiety disorders share a common etiological factor⁴¹, or that pediatric functional abdominal pain and anxiety in fact represent different aspects of the same disorder.⁴² In child psychiatry, “internalizing disorders” comprise anxiety disorders, depressive disorders, and somatoform disorders. Although these three groups of disorders can be distinguished according to their phenomenology according to current diagnostic systems, such as DSM-IV³⁶, they share a high degree of comorbidity and may share a common genetic background.^{43, 44} A main question to be resolved is whether patients with functional abdominal pain suffer from a hypersensitivity for physical stimuli restricted to the viscera or whether this hypersensitivity has a more general character⁴⁰, like is presumed in children with anxiety disorders.⁶

The startle reflex

A startle reflex is a rapid, involuntary contraction of the skeletal and facial muscles in response to abrupt and intense stimulation.⁴⁵ It is a common reaction in animals and humans, presumably preparing the subject to respond by fighting or by escape as quickly as possible. The startle reflex is a generalized flexion response, with the reaction most prominent around the face, neck and shoulders, and less marked in the lower part of the body. Stimuli of different sensory modalities can provoke the response and, regardless of sensory modality, the intensity of the surprise reaction decreases with repeated stimulation in healthy subjects.⁴⁶ Depending on the intensity of the stimulus this generalized response is almost entirely extinguished after 4 to 6 stimuli in normal subjects, with the neck (sternocleidomastoid) muscle activity as the last component to disappear (the blink response persists).⁴⁷ The startle reflex

occurs in almost all species, including humans. It can be elicited in children⁴⁸ and adolescents⁴⁹; it develops after 2-4 months of age, and coincides with the regression of the Moro reflex.⁵⁰

The auditory startle reflex (ASR) in humans was originally described by Landis and Hunt in 1939⁵¹ and delineated more extensively in later reports.^{45, 47, 52} The ASR is mediated by a simple three-synapse neuronal circuit located in the lower brainstem.⁵³ The medial bulbopontine reticular formation, particularly the nucleus pontis caudalis, is considered the primary center subserving the ASR.^{54, 55} The bulbospinal reticular formation receives not only direct subcortical inputs but also indirect inputs from the cerebral cortex, limbic system and basal ganglia. Electromyographic (EMG) methods proved helpful in defining the ASR in more detail. EMG is the study of muscle function using electrical signals from muscles. In surface EMG the electrical signal is measured using electrodes fastened to the skin overlying the muscle of choice. EMG studies showed that the ASR has a duration of 0.3 -1.5 s, depending upon its intensity.⁴⁵ The reflex nature of the ASR is borne out by its short latencies and by the observations that cognition does not modulate it, that it is the initial response in all subjects and that it cannot be totally inhibited or correctly simulated.^{56, 57} The overall pattern of the response to sound is distinctive and stereotyped.⁴⁵ It commences proximally with an eye-blink response and facial grimace, and spreads distally to produce upper-limb, truncal and lower-limb flexion.⁵⁶ The latencies of responses in trunk and limb muscles increase with the distance of their respective segmental innervations from the caudal brainstem (from central to peripheral muscle groups). The blink reflex typically consists of a burst of orbicularis oculi EMG activity at a latency of about 20-50 msec in human adults, depending on the eliciting stimulus.^{37, 50} The response latency in quadriceps femoris is about 110 ms.⁴⁵ Responses are observed in the masseter, deltoideus, biceps brachii, abductor pollicis brevis, rectus abdominis, quadriceps, rector femoris, tibialis anterior, soleus (Figure 3).^{47, 58}

In reporting startle, subjects do not necessarily distinguish between motor, emotional and autonomic responses. The ASR consists of the initial flexor motor response which follows a similar though not identical pattern between individuals.⁵⁶ This motor response is followed by autonomic responses, having longer latency and longer duration.⁵⁶

The term “startle modification” refers to the changes in the occurrence, magnitude and/or the latency of a startle reflex. Startle reflexes are not simple, fixed, and invariant reactions to stimuli.⁵⁰ The form of the ASR is complicated and varies under different conditions. Alertness, emotional state, stimulus strength and repetition, the

presence of tonic voluntary muscle activity, incipient movement and posture may all modify the response. Therefore the ASR can be 'primed' (i.e. the activation level of the response can be raised) by certain prior stimuli or states. For this reason the ASR is often used in research to index brain processes and also to demonstrate the effect of stimuli or conditions (producing changes in subsequently elicited startle reflexes) on

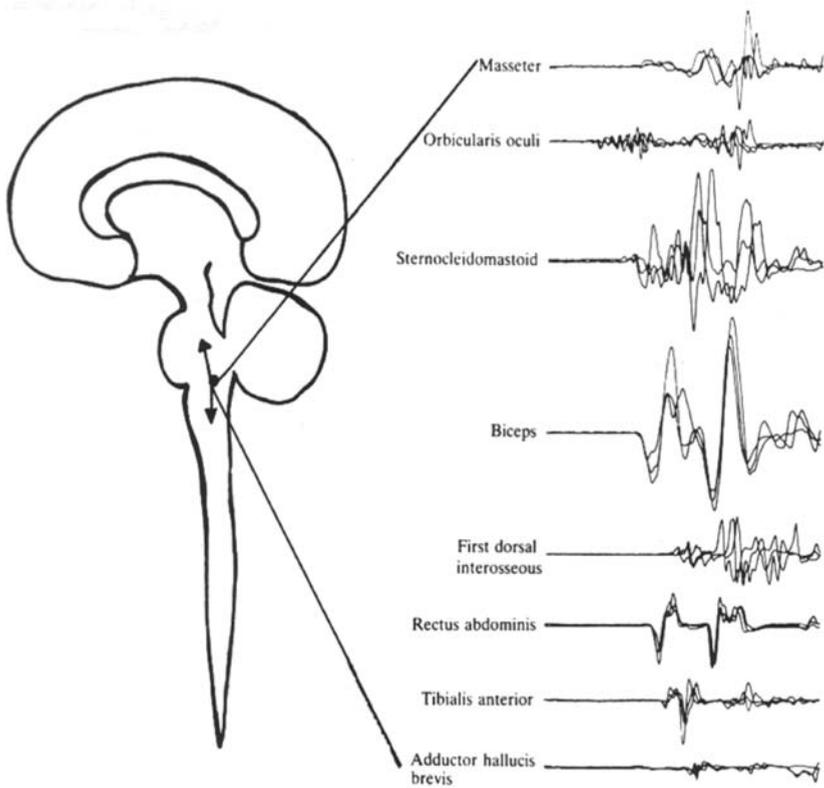


Figure 3. The auditory startle reflex

those brain processes.⁵⁰ For example, the magnitude and habituation of the ASR vary with the presentation of distraction or warning stimuli.⁵⁹ The ASR therefore indexes the capacity of the subject to filter or react to relevant stimuli.⁶⁰ Further, the ASR is highly sensitive to processes such as habituation and sensitization.⁴⁵ Finally, fatigue and stress predisposes to increased ASR's.⁶¹ Therefore the ASR provides a window onto brain processes related to the fear response in humans.⁵⁰ The fact that the ASR has a distinctive pattern⁵¹, is a basic physiological response and always occurs in combination with or as a result of a fear reaction⁶² makes it unique in emotion research. Further, the startle stimulus is easily elicited, nonverbal, culture-free, quantifiable⁵⁰ and can be evoked at will during any condition. The simplicity of the underlying processes and the fact that the ASR is preattentive and not under volitional

control makes it an attractive measure. Nowadays, affective modification of the ASR has become a major research tool in a large number of laboratories. When instigated independently, the 'baseline' ASR not manipulated by experimental conditions, it is used especially as an instrument in neuropsychiatric research, for example to study patients with neurological⁶³ or psychiatric disorders.³⁷

The eye blink response, or auditory blink response, is the most commonly used measure of the ASR in human research today.^{37, 64, 65} However, several authors have pointed out that the EMG activity recorded in the orbicularis oculi muscle often contains two responses: a short and a long latency response.^{45, 47, 47, 66-71} In accordance, a distinction between an early audiogenic blink reflex and a ASR in the orbicularis oculi was made.⁴⁷ This was also based on the fact the early auditory blink reflex can be registered in the orbicularis oculi muscle without concomitant EMG activity in other craniocervical muscles.⁴⁷ It was concluded by at least one startle expert, Peter Brown, that not all changes in the EMG activity of the orbicularis oculi can be viewed as effects on the ASR.⁴⁷ In addition, it was suggested that the early blink reflexes are controlled at the bulbopontine level by the brainstem startle center, whereas the ASR flexor reactions are controlled at the mesencephalic level by the midbrain reticular formation and inferior colliculus.^{47, 72} Therefore it has been recommended that the ASR should be assessed by recording the activity of several muscles instead of just one.⁴⁷

Aims and outline of the present thesis

In this thesis we will use the following definition of the ASR: 'rapid, involuntary contraction of the skeletal and facial muscles following sudden and intense auditory stimulation'.⁴⁵ Although the autonomic response following auditory stimuli is considered part of the ASR by several authors, in this study the definition of the ASR will be limited to the motor response. We will use the sympathetic skin response to index the autonomic response following the auditory stimuli separately.

The current thesis has two principal aims. The first aim concerns the use of the ASR as a research tool in healthy children and children with neuropsychiatric disorders. A first question is whether the ASR measured over multiple muscles is better than restricting the measurement to the blink response. In adults the ASR measured over multiple muscles is suggested to be a more complete and pure representation of the ASR. Our hypothesis is that also in children "the multiple muscle ASR" or the ASR occurring in the whole body will prove to be superior to the "single muscle ASR" or blink response. Based on the literature we will use differences between the multiple muscle ASR and the blink response to argue that the ASR measured over multiple muscles is a better tool for startle

studies in children. In contrast, similar results will be interpreted as supporting the use of the blink response only. That is, we propose that the blink response can be considered a valid representation of the ASR in this population if it yields similar results as the ASR measured over multiple muscles. Secondly, general characteristics of the two ASR parameters will be described in children. Details of the ASR, e.g. the startle pattern and muscle latencies, are explored that are usually not reported in psychophysiological ASR studies. This approach enables a comparison with previous extensive polymyographic EMG studies of other startle syndromes of which the etiology is sometimes more clearly delineated.

The second aim of this thesis concerns the investigation of the ASR in children with anxiety disorders and children with functional abdominal pain in order to gain knowledge on the etiology of these disorders. As the anatomical structures which are involved in generating and modulating the ASR are known, the ASR as a possible endophenotype or biomarker may contribute to the knowledge on the etiology of these disorders. We hypothesize that ASR abnormalities will occur in both disorders, but more prominently so in children with anxiety disorders. Secondly, we aim to follow the change of the possible ASR abnormalities when the anxiety disorder patients have been successfully and unsuccessfully treated with cognitive-behavioral therapy.

The tendency to startle in the population varies greatly, with some individuals aptly described as “hyperstartlers”. Startle syndromes are heterogeneous and the different types are considered to develop as a result of genetic mutations, brain damage, psychiatric disorders and environmental or cultural factors. An overview of these different startle syndromes is given (**chapter 2**). The auditory blink response, used in psychiatric startle studies, and the ASR measured over multiple muscles, used in neurological startle studies, were investigated in healthy children (**chapter 3**). Although there is no gold standard to measure the ASR, it is possible to discern differences in habituation, sex and age effects between these measures. In addition, in the following chapters (**chapter 4, 5 and 6**) both the multiple muscle ASR and the blink response are investigated in clinical populations. In these chapters the ASR and autonomic sympathetic skin response are described for children with anxiety disorders and children with functional abdominal pain compared to controls. Moreover, the children with anxiety disorders and controls were assessed again after a period of 12 weeks in which the patients were treated (**chapter 5**). In a case study of a very rare neurological startle syndrome, hyperekplexia (**chapter 7**), the ASR and psychiatric symptoms before and after treatment were described. Finally anxious and negative cognitions and several other psychological characteristics of children with functional abdominal pain are compared to those in children with anxiety disorders and controls (**chapter 8**).