CHAPTER 1

General Introduction
INTRODUCTION

Motor development in children
Evaluation of motor development is one of the most important aspects in the general assessment of a child’s development. It not only provides information about possible developmental delay and integrity of the nervous system, but it may also reflect cognitive and social functioning of the child. For example, at school age, a child’s social role depends heavily on how well it can participate in games and sports. Normal motor development is characterized by large intra-individual and inter-individual variability. The Neuronal Group Selection Theory categorizes the intra-individual variability in three independent stages with separate mechanisms underlying the variability in motor performance. During primary variability, which occurs during fetal life and infancy (0-2 years), the neural system explores all possibilities of motor behavior according to epigenetically determined, roughly specified ‘primary neural repertoires’. Primary variability is followed by the stage of selection, which occurs during infancy at function-specific ages. There will be a minor reduction in motor variability, due to experience driven selection of the most effective motor patterns and their associated neuronal groups. The final stage of secondary or adaptive variability occurs during mid-infancy, flourishes at 2-3 years and matures into adolescence. During this stage, based on a myriad of experiences, ‘secondary neural repertoires’ are formed to adapt each movement exactly and efficiently to task-specific conditions. Variability in motor development is present until late childhood/adolescence.

The inter-individual variability partly depends on genetic factors which determine the speed of neurodevelopmental processes. Motor behavior of the newborn is predominantly under control of the spinal cord and medulla. This is represented by, for example, the appearance of primitive reflexes. Some of these reflexes will form preliminary patterns of future voluntary actions, such as the asymmetric tonic neck reflex (reaching), the stepping reflex (walking) and the palmar grasp (grasping). When cortical brain centers mature, integration with subcortical areas of the brain start to inhibit the primitive reflexes, resulting in their disappearance. Soon after birth, infants begin to acquire motor milestones such as smiling, keeping head balance, grasping, sitting, walking and improving fine movement skills. Depending on genetic and extrinsic factors, the age at which specific motor milestones are acquired is quite variable (inter-individual variability). However, common and specific developmental patterns exist. For example, motor control of trunk and arms is reached before control over legs and finger movements. This is related to the maturation pattern of the cerebral cortex, which start with the upper, central and hindmost cerebral cortex, followed by the frontal and lower temporal lobes. Other neurodevelopmental processes that improve motor function in the developing child are cerebellar growth, selective elimination of abundant neuronal connections and myelination of the central and peripheral nervous system. The cerebellar vermis grows until eight years of age, whereas the anterior and superior posterior regions of the cerebellar hemispheres continue to develop until the 14th-17th year of age. PET studies indicate that the elimination of redundant synapses may continue until the end of adolescence.
while ongoing myelination enhances neural conduction speed from childhood to adulthood.\textsuperscript{8,9} Such data implicates that physiological improvement of motor performance can be seen until late into childhood/adolescence.

**Coordination**

Coordination involves the interaction between different muscles and body parts to perform effective goal-directed movements. Different reference systems are used to accomplish this task. Extrinsic reference systems relate objects in the outside world to other objects or to our body.\textsuperscript{10} Exteroceptive information, such as visual and auditory information, is crucial for these systems. Intrinsic reference systems relate body parts to other body parts and involve aspects such as the configuration of muscle lengths or the configuration of joint angles. These are primarily based on proprioceptive information from the body.\textsuperscript{10} Proprioceptive information is provided by muscle spindles (sensitive to muscles length) and Golgi tendon organs (sensitive to muscle tension).\textsuperscript{11} The cerebellum integrates the information of the different reference systems. Its exact physiological functions and modes of operation are still under investigation. An influential theory states that in the cerebellum predictive forward models for motor control are generated.\textsuperscript{12,13} Not only coordination itself, but also motor learning are cerebellar functions.\textsuperscript{14} Recently, the role of the cerebellum in cognitive processing has come to the forefront as well.\textsuperscript{14,15}

Although the cerebellum contains only 10% of the total brain volume, more than half of the neurons of the brain are located in the cerebellum.\textsuperscript{14} The cerebellum consists of grey matter in the cerebellar cortex, the internal white matter and the deep nuclei. It can be divided in three functional regions (Fig 1).\textsuperscript{14} The *vestibulocerebellum* participates in balance and eye movements. The *spinocerebellum*, consisting of the midline vermis and the intermediate hemispheres, participates in the motor control of the trunk, the proximal muscles and the eye movements (vermis) and in the motor control of the distal muscles of the limbs and the digits (intermediate hemispheres). The *cerebrocerebellum* (lateral hemispheres) has an important role in planning, motor learning and execution of motion, but possibly also in non-motor functions such as working memory.\textsuperscript{14,15} Afferent input to these functional regions, relevant for motor performance, originates from cell bodies in the spinal cord and the brainstem. The afferent input carries information from the periphery and from many brain structures, such as the sensory, motor and visual cortex and the vestibular system (Fig 1).\textsuperscript{14,16} Due to an intricate local network structure, afferent information to the cerebellum is compared in both the cerebellar cortex and the deep nuclei.\textsuperscript{14} Efferent neurons from the deep nuclei connect to the ventrolateral thalamus, red nucleus, reticular nuclei and vestibular nuclei. These structures then target the motor, prefrontal, premotor and parietal cerebral cortices, the motor and interneurons of the spinal cord and multiple brainstem nuclei (Fig 1).\textsuperscript{14} Several recurrent closed loops connect the cerebellum with the cerebral cortex, which enables constantly updated communication between specific parts of the cerebellum with specific parts of the cerebral cortex.\textsuperscript{14} Altogether, the cerebellum provides continuously adapted information for balance control and
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decision-making regarding speed, force and direction of intended movements. In this way the cerebellum provides a frame-work for fine-tuning intended goal-directed movements.

**Ataxia**

The term ‘ataxia’ refers to an impairment of the smooth performance of intended goal-directed movements, resulting in impaired coordination as defined by repeated deviations of expected limb, trunk and eye movements and slurred speech (dysarthria). A delayed initiation of response is also part of ataxia. Ataxia occurs when the cerebellum is damaged or when the sensory input to the cerebellum is impaired. Concurrent central hypotonia may exist (decreased muscle tone due to damage to the central nervous system). Somewhat confusingly, ‘ataxia’ is also used to indicate

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**Figure 1.** The functional regions reveal different structured pathways of input and output targets. The schematic cerebellum is unfolded (Based on Lisberger et al, in: Kandel, Principle of Neuroscience, 2012)
diseases – nosological entities – in which ataxia, the phenomenon of impairment of goal directed movements, is a prominent disease manifestation.

Currently, the ‘gold standard’ for the diagnosis of the phenomenon ‘ataxia’ is phenotypic recognition by neurologists, based upon a number of qualitatively defined clinical tests. In adult onset ataxia (abbreviated in this thesis as AOA) caused by diseases such as Multiple Sclerosis, paraneoplastic cerebellar degeneration, Multiple Systems Atrophy and hereditary neurodegenerative diseases, this might be convenient. However, in diseases with onset in early life, i.e. before 25 years of age (early onset ataxia, or in this thesis: EOA), the recognition of ataxia may be difficult for several reasons. First, immature motor behavior may mimic features of (cerebellar or sensory) ataxia. This is reflected by an age-related decline of ataxia rating scale scores in healthy children until they reach adult performance around age 14.21,22 Especially in children until 6 years of age, agreement among rating clinicians about ataxia rating scale scores was fair to moderate, only.22 This indicates that ataxia recognition at a young age might be even more challenging. Second, other developmental or medical conditions might present with phenotypically impaired coordination that resembles ataxia. For example, the motor behavior of children with developmental coordination disorder (DCD) is characterized by clumsiness, slowness and inaccurately performed motor skills in the absence of intellectual disability, visual impairment or a neurological condition that affects movement.23 Literature suggests that the cerebellum might be involved, as DCD is associated with problematic sensorimotor integration, postural control, motor learning, strategic planning, visual-spatial processing and executive functioning.23-25 Peripheral hypotonia, being reduced muscle tone due to conditions of the peripheral neuromuscular system, may also resemble ataxia. For instance, muscle weakness or joint hyperlaxity in connective tissue disorders may impair balance.26-28 Third, recognition of phenotypic ataxia may be difficult if there is a co-existence of other neurological movement abnormalities such as dystonia, chorea, myoclonus or tremor. This situation arises in many early onset genetic neurodegenerative diseases of the nervous system.29-32 Particularly in young children, it can be challenging to distinguish ataxia from other conditions and causes of impaired coordination.

**Importance of Phenotypic Recognition of Early Onset Ataxia**

Ataxia in childhood is a rare phenomenon. After excluding acquired ataxia (infections, tumors, cerebral palsy and pediatric multiple sclerosis), the overall prevalence of genetic diseases with ataxia as a prominent feature is estimated to be 14.6/100.000.33 This prevalence includes many rare and heterogeneous disorders.33 Thanks to modern genetic technology, the identification of novel mutations in new genes and the identification of additional phenotypes associated with already known mutations proceeds at an accelerating speed. Particularly the application of next generation sequencing techniques has facilitated molecular diagnostics.34 To gain more insight into the often unknown etiology, natural history and treatment options of the many EOA causes, European ataxia interest groups have set out to assemble a single longitudinal ataxia database that includes pediatric as well as adult patients.22 This database will associate rare phenotypes with
recently found genes or with newly discovered phenotypes of known genes. Also, DNA sequences of patients with similar (rare) phenotypes can be compared, which will result in the discovery of additional and novel genetic disorders. Centralizing information of patients with EOA will increase our understanding of the natural history of rare EOA disorders, and thus improve our counseling efforts of patients and their families. Ultimately, this expanding body of knowledge will be crucial in designing and testing novel treatment strategies for patients with various ataxia disorders. Such databases underlie efficient patient identification and inclusion for clinical trials. But in order to obtain a high-quality database, accurate phenotyping of ataxic patients is of utmost importance.

**Importance of Reliable Ataxia Rating Scales in Early Onset Ataxia**

Measurement of ataxia severity is one of the primary end points during follow-up of natural history cohorts and in clinical trials. Currently, ataxia rating scales administered by clinicians are used to measure ataxia severity. Frequently applied ataxia rating scales are the Friedreich Ataxia Rating Scale (FARS)\(^3\), the International Cooperative Ataxia Rating Scale (ICARS)\(^3\)\(^6\) and the Scale for Assessment and Rating of Ataxia (SARA).\(^3\)\(^7\) For these three scales, good characteristics have been demonstrated in adult patients regarding reliability and validity.\(^3\)\(^8\) The FARS and ICARS are quite labor intensive, taking about 30 and 22 minutes, respectively, to complete. The SARA is shorter, with an average of 14 minutes completion time. Due to this brief assessment time, the SARA is easier to apply in clinical practice and might be suitable for children with a shorter attention span. However, SARA’s reliability and validity have hardly been assessed in children with EOA. Given the considerations of the difficulties in assessing ataxia in EOA as outlined previously, we cannot assume similar test characteristics of these ataxia rating scales in children as they have been developed and characterized in adults. In adults, ataxia appeared to be the only influencing factor of the SARA score – exactly what the instrument intended to measure.\(^3\)\(^9\) However, we have generated data that demonstrate that in the pediatric population ataxia rating scales are influenced by other factors besides ataxia.\(^2\)\(^1\),\(^2\)\(^2\),\(^2\)\(^3\)\(^9\) Ataxia rating scales appear age-dependent in healthy children, warranting age-related SARA reference values for reliable interpretation of longitudinal SARA scores in young children with EOA.\(^2\)\(^1\),\(^2\)\(^2\) Moreover, as concurrent movement disorders also affect coordination, we expect that they will affect ataxia rating scale scores as well. Finally, in children with Friedreich’s Ataxia, ICARS scores appeared to be confounded by muscle weakness.\(^3\)\(^9\) Therefore, insight in the reliability and validity of ataxia rating scales in children with ataxia is important for reliable ataxia measurement and follow up.

**Aims of the thesis**

The aim of this thesis is twofold. First, we want to investigate the reliability of phenotypic ataxia recognition in EOA and to search for hallmarks that support phenotypic ataxia recognition in this group of patients. Second, we aim to study the reliability and validity of the SARA in patients with EOA.
Outline of the thesis

The first part of this thesis (chapters 2-5) deals with the ‘Phenotypic assessment of impaired coordination in children’. In chapter 2, we examine the reliability of phenotypic ataxia recognition in patients referred for EOA. We also explore whether certain clinical hallmarks may support phenotypic ataxia recognition in this population. In chapter 3 and chapter 4, we investigate whether movement sensors (applied during SARA assessment) are able to support phenotypic recognition of impaired coordination in a cohort of children with ataxia, DCD and healthy children. In chapter 5, we first investigate the reliability of EOA recognition in a cohort of children with impaired coordination due to EOA, DCD or hypotonia or hypoactive muscle activation (HHM). We explore whether there are clinical features that may help to distinguish between ataxia and DCD.

The second part of the thesis focuses on the ‘Quantitative assessment of impaired coordination in children’. In chapter 6, we present the results of the European SARA Age-Validation Trial in healthy children, to provide age-related reference values of SARA scores. In chapter 7, we investigate the reliability and validity of ataxia rating scales in patients with EOA, focusing on the inter- and intra-observer agreement and on the influence of concurrent movement disorders on the ataxia rating scales. Finally, in chapter 8, we investigate the validity of the SARA gait subscore in patients with heterogeneous causes of EOA. We examine correlations between the SARA gait subscore and other measurements of coordination. We also explore whether myoclonus and muscle weakness influence SARA gait subscores in patients with heterogeneous causes of EOA.

In chapter 9, we summarize our results, offer comparisons with existing literature, and discuss the strengths and limitations of our results. Suggestions for future research are offered.
REFERENCES


PART I

Phenotypic assessment of impaired coordination in children