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**Development of hand function and stereotypies in
Rett Syndrome during the first year of life**

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*Dedicated to the
study participant
and her family.*



*Der Studienteilnehmerin
und ihrer Familie gewidmet*

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Zusammenfassung

Hintergrund: Zu den typischen Symptomen von Rett Syndrom gehört der Verlust der Handfunktion innerhalb der ersten 18 Lebensmonate und das etwa gleichzeitige Auftreten erster zwanghafter waschender und wringender Handbewegungen. **Ziel** dieser Studie war es, die Entwicklung von normalen und abnormalen Handbewegungen innerhalb des ersten Lebensjahres zu analysieren. **Material und Methoden:** Die Eltern eines Mädchen mit klassischem Rett Syndrom und nachgewiesener *MECP2* Mutation haben ihre privaten Videoaufnahmen, die sie während des ersten Lebensjahres im Vertrauen auf eine normale Entwicklung ihres Kindes gemacht haben, der wissenschaftlichen Analyse zur Verfügung gestellt. In insgesamt 267 Sequenzen mit einer jeweiligen Dauer von 10 Sekunden bis 4 Minuten war mindestens eine Hand gut sichtbar, um Hand- und Fingerbewegungen und -haltungen genauest analysieren zu können. **Ergebnisse:** Es wurden 19 normale und 12 abnormale Bewegungsmuster beobachtet. Das Mädchen erreichte sämtliche Meilensteine der feinmotorischen Entwicklung wie etwa das Führen der Hände zur Mittellinie, das Transferieren von Gegenständen, den Pinzettengriff, das Deuten mit dem Zeigefinger und das Umblättern von Buchseiten. Bereits ab dem 2. Lebensmonat waren jedoch auch abnormale Hand- und Fingerbewegungen zu sehen: Ein kurzer, feinschlägiger Tremor der Arme und Hände wurde ab der 5. Lebenswoche wiederholt beobachtet. Ab der 7. Lebenswoche zeigte das Mädchen eine abnormale Haltung des Daumens. Die ersten Handstereotypien traten bereits während des 5. Lebensmonats auf: Ab dem Alter von 18 Wochen wurden abnormale Drehungen des Handgelenks beobachtet und ab der 22. Lebenswoche zeigte die Studienteilnehmerin repetitives Öffnen und Schließen beider Hände. Waschende Handbewegungen waren erstmals im Alter von 32 Wochen (8 Monaten) zu sehen, wobei während der gleichen Sequenz auch normale Fingerbewegungen auftraten. In jedem Monat hatte die Studienteilnehmerin sowohl normale als auch abnormale Handbewegungen, letztere jedoch in einer geringeren Häufigkeit als normale Bewegungen. **Schlussfolgerung:** Unsere akribisch durchgeführte Studie ist ein wichtiger Beitrag zur Widerlegung der Meinung, dass die Entwicklung vom Mädchen mit Rett Syndrom innerhalb der ersten 6 bis 18 Monate unauffällig verläuft. Die Hypothese, dass normale Handbewegungen mit dem Alter abnehmen und abnormal Handmuster gleichzeitig zunehmen, konnten wir nicht bestätigen.

Abstract

Background: One of the specific signs of Rett Syndrome is the loss of functional hand use within the first 18 months of life, followed by compulsive hand movements such as wringing and washing. **Aim** of this study was to analyse the development of both normal and abnormal hand movements within the first 12 months of life. **Material and Method:** Twohundred-sixty-seven family video sequences (duration: 10 seconds to 4 minutes) of a girl with classic Rett Syndrome (*MECP2* mutation-positive) were carefully analysed for hand movements and postures. **Results:** Nineteen normal and twelve abnormal patterns were observed in each hand. Although the girl fulfilled all developmental milestones such as hand-to-midline, transfer of objects, pincer grasp, index finger pointing or turning pages, abnormal hand and finger movements have been noted from 5 weeks onwards. The first abnormalities were short tremulous hand movements followed by an abnormal thumb posture from 7 weeks onwards. The first hand stereotypies occurred already during the 5th month of life: From 18 weeks onwards the girl showed abnormal rotations of the wrist and from 22 weeks onwards repetitive opening and closing of the hands was observed. The first washing movements were seen at 32 weeks (8 months) although at the same age the girl showed variable finger movements. Both abnormal and normal hand patterns were present during each month of the observation period. However the consistency of normal patterns was always higher than that of abnormal behaviours. **Conclusion:** Our meticulous and close follow-up study is a further contribution to refute the paradigm of a seemingly inconspicuous early development. Yet, we could not confirm the hypothesis that abnormal behaviours would increase and normal patterns would decrease with age.

Introduction

Rett Syndrome (RTT) is a severe neurodevelopmental disorder which was first described by Andreas Rett in 1966^[1,2]. Affecting mainly females with an estimated prevalence of about 1 in 10.000 adolescent girls^[1,3,4], it is thought to be the second most common genetic cause of cognitive impairment in females after Down Syndrome^[4-6]. In 1999, the disorder was for the first time associated with mutations in the *MECP2* gene, encoding for the methyl-CpG-binding protein 2^[7]. Extensive genetic testing has led to the detection of a mutation in this gene in about 95% of all patients with classic RTT^[8,9]. Still, the diagnostic criteria for the impairment remain to be based exclusively on the patients' clinical presentation as some individuals with RTT are mutation- negative and *MECP2* mutations have been found in people without the clinical phenotype of RTT^[10-12].

After an apparently normal development for the first 6 to 18 months of life, the patients enter a period of regression during which they lose previously acquired speech and fine motor skills and develop stereotypic hand movements^[1,10,13,14]. Behavioural abnormalities are also prominent during this stage. The patients often withdraw from their environment and become agitated, irritable and frightened^[1,14,15].

At around the age of 5 years the girls' condition usually tends to stabilise and they become more interested in their surroundings^[1,14]. However, speech and purposeful hand use usually remain absent while hand stereotypies continue and other symptoms such as epilepsy, scoliosis, breathing abnormalities, gastrointestinal disturbances and severe cognitive impairment develop^[16-25]. Parents also commonly report behavioural peculiarities such as inappropriate screaming, crying and unusual night laughter^[14,26]. Gait is often ataxic and unstable and ambulation is usually lost as the disease progresses^[1,14,19,27].

Initially, the patients have been thought to develop normally during the first 6 to 18 months of life^[28], yet extensive research within the last decade has brought growing evidence of developmental deviations and abnormal behaviours already from early infancy onwards. Delays in the achievement of motor milestones, abnormal general movements, peculiarities in speech development and unusual behaviours have been reported^[1,29-38]. Although some researchers have also described peculiar postures and movements of the hands^[33-38], our study was the first to focus exclusively on the development of hand function and stereotypies in RTT. Our intent was to analyse the development and trajectories of both normal and abnormal hand movements and postures during the first year of life. We

providentially had access to extensive home video recordings of a girl who later was diagnosed with classic RTT. The videos included 365 minutes (6 hours and 5 minutes) of recordings in which at least one hand was accessible for observation. These were meticulously analysed for our study.

This thesis is divided into two parts: Chapter one “What is RTT?” gives an overview about the clinical features and the pathophysiology of RTT. The description and the results of our case study are outlined in chapter two “Case study”.

References for Introduction

- [1] Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.1-26.
- [2] Haas RH. Andreas Rett. In: Ashwal S, editor. *The Founders of Child Neurology*. San Francisco: Norman Publishing; 1990. p.822-3.
- [3] Laurvick CL, de Klerk N, Bower C, Christodoulou J, Ravine D, Ellaway C, et al. Rett syndrome in Australia: a review of the epidemiology. *J Pediatr* 2006;148(3):347-52.
- [4] Hagberg B. Rett syndrome: clinical peculiarities and biological mysteries. *Acta Paediatr* 1995;84(9):971-6.
- [5] Hagberg B, Goutières F, Hanefeld F, et al: Rett syndrome: Criteria for inclusion and exclusion. *Brain Dev* 1985;7:372-3.
- [6] Ellaway C, Christodoulou J. Rett syndrome: clinical update and review of recent genetic advances. *J Paediatr Child Health* 1999;35:419-26.
- [7] Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;23(2):185-8.
- [8] Amir R, Sutton V, Van den Veyver I: Newborn screening and prenatal diagnosis for Rett syndrome: implications for therapy. *J Child Neurol* 2005;20:779- 83.
- [9] Temudo T, Santos M, Ramos E, Dias K, Vieira JP, Moreira A, et al. Rett syndrome with and without detected MECP2 mutations: an attempt to redefine phenotypes. *Brain Dev* 2011;33(1):69-76.
- [10] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;68(6):944-50.
- [11] Sanmann JN, Schaefer GB, Buehler BA, Sanger WG. Algorithmic approach for methyl-CpG-binding protein 2 (MECP2) gene testing in patients with neurodevelopmental disabilities. *J Child Neurol* 2012;27(3):346-54.
- [12] Webb R, Wren JD, Jeffries M, Kelly JA, Kaufman KM, Tang Y, et al. Variants within MECP2, a key transcription regulator, are associated with increased susceptibility to lupus and differential gene expression in patients with systemic lupus erythematosus. *Arthritis Rheum* 2009;60(4):1076-84.
- [13] Hagberg B, Witt Engerström I. The Swedish series of females with Rett syndrome 1960-92. In: Hagberg B, editor. *Rett syndrome - clinical and biological aspects*. London: Mac Keith Press; 1993. p.21-6.
- [14] Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002;8:61-5.
- [15] Larsson G, Lindström B, Engerström IW. Rett syndrome from a family perspective: The Swedish Rett Center survey. *Brain Dev* 2005;27 Suppl 1:14-9.
- [16] Kerr AM, Montague J, Stephenson JB. The hands, and the mind, pre- and post-regression, in Rett syndrome. *Brain Dev* 1987;9(5):487-90.
- [17] Temudo T, Oliveira P, Santos M, Dias K, Vieira J, Moreira A, et al. Stereotypies in Rett syndrome: analysis of 83 patients with and without detected MECP2 mutations. *Neurology* 2007;68(15):1183-7.
- [18] Downs J, Bebbington A, Kaufmann WE, Leonard H. Longitudinal hand function in Rett syndrome. *J Child Neurol* 2011;26(3):334-40.
- [19] Hagberg B.J. Rett syndrome: long-term clinical follow-up experiences over four decades. *Child Neurol* 2005;20(9):722-7.
- [20] Didden R, Korzilius H, Smeets E, Green VA, Lang R, Lancioni GE, et al. Communication in individuals with Rett syndrome: an assessment of forms and functions. *J Dev Phys Disabil* 2010;22(2):105-18.
- [21] Julu PO, Kerr AM, Apartopoulos F, Al-Rawas S, Engerström IW, Engerström L, et al. Characterisation of breathing and associated central autonomic dysfunction in the Rett disorder. *Arch Dis Child* 2001;85(1):29-37.
- [22] Koop SE. Scoliosis and Rett syndrome. *Dev Med Child Neurol*. 2011;53(7):582-3.
- [23] Steffenburg U, Hagberg G, Hagberg B. Epilepsy in a representative series of Rett syndrome. *Acta Paediatr* 2001;90(1):34-9.
- [24] Motil KJ, Caeg E, Barrish JO, Geerts S, Lane JB, Percy AK, et al. Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome. *J Pediatr Gastroenterol Nutr* 2012;55(3):292-8.

- [25] Baptista PM, Mercadante MT, Macedo EC, Schwartzman JS. Cognitive performance in Rett syndrome girls: a pilot study using eyetracking technology. *J Intellect Disabil Res* 2006;50(Pt 9):662-6.
- [26] Mount R, Hastings R, Charman T, reilly S, Cass H. Behavioural and emotional features of Rett syndrome. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.339-42.
- [27] Downs JA, Bebbington A, Jacoby P, Msall ME, McIlroy O, Fyfe S, et al. Gross motor profile in Rett syndrome as determined y video analysis. *Neuropediatrics* 2008;39(4):205-10.
- [28] Hagberg B, Goutières F, Hanefeld F, Rett A, Wilson J. Rett syndrome: criteria for inclusion and exclusion. *Brain Dev* 1985;7(3):372-3.
- [29] Leonard H, Moore H, Carey M, Fyfe S, Hall S, Robertson L, et al. Genotype and early development in Rett syndrome: The value of international data. *Brain Dev* 2005;27 Suppl 1:59-68.
- [30] Nomura Y. Early behaviour characteristics and sleep disturbance in Rett syndrome. *Brain Dev* 2005;27 Suppl 1:35-42.
- [31] Segawa M. Early motor disturbances in Rett syndrome and its pathophysiological importance. *Brain Dev* 2005;27 Suppl 1:54-58.
- [32] Einspieler C, Kerr AM, Prechtl HF. Abnormal general movements in girls with Rett disorder: the first four months of life. *Brain Dev* 2005;27 Suppl 1:8-13.
- [33] Temudo T, Maciel P, Sequeiros J. Abnormal movements in Rett syndrome are present before the regression period: a case study. *Mov Disord* 2007;22(15):2284-7.
- [34] Einspieler C, Kerr AM, Prechtl HF. Is the early development of girls with Rett disorder really normal?. *Pediatr Res* 2005;57(5):696-700.
- [35] Burford B, Kerr AM, Macleod HA. Nurse recognition of early deviation in development in home videos of infants with Rett disorder. *J Intellect Disabil Res* 2003;47(8):588-96.
- [36] Marschik PB, Pini G, Bartl-Pokorny KD, Duckworth M, Gugatschka M, Vollmann R, et al. Early speech-language development in females with Rett syndrome: focusing on the preserved speech variant. *Dev Med Child Neurol* 2012;54(5):451-456.
- [37] Marschik PB, Einspieler C, Oberle A, Laccone F, Prechtl HF. Case report: Retracing atypical development: a preserved speech variant of Rett syndrome. *J Autism Dev Disord* 2009;39(6):958-61.
- [38] Burford B. Perturbations in the development of infants with Rett disorder and the implications for early diagnosis. *Brain Dev* 2005;27 Suppl 1:3-7.

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1 What is RTT?

1.1 History of RTT

1.1.1 Discovery of RTT

Rett Syndrome (RTT) is named after Andreas Rett (Figure 1.1), an Austrian paediatrician, who practised in Vienna after World War II. Facing a society with great neglect for the disabled, Rett dedicated his work to young handicapped people, establishing an institution for treatment and care of these children in Lainz, Austria in 1956. Today, the physician is known as the pioneer in child neurology in Austria^[1,2].



Figure 1.1: Andreas Rett[4].

It was in 1965, when Rett coincidentally watched two of his female patients performing wringing and washing movements with their hands. Curiosity prompted him to look through his other patients' files and he found further girls with similar symptoms^[2,3]. He later described his discovery of the disease as follows:

"One day in the spring of 1965, two mothers holding their children on their laps were sitting in the waiting room. Both children were swaying and the mothers held their arms. Both children, who were treated for epileptic seizures, were well known to me. That morning I passed by them repeatedly and, incidentally, the mothers let go of their children's arms. At once, the children put their hands together and started nearly identically-looking washing movements. I asked the mothers not to stop these movements again, and was startled at the similarities. It was the same gaze, same facial expression, same weak muscles and the same

stereotyped movements of their hands. Moreover, they were both females. At first, I was amazed by this enormous coincidence and thought I must have come across several other children with these symptoms. I asked my head nurse to look at these children and she immediately recalled some more names of children who behave similarly. We invited them, placed them next to each other and found that all of them showed the same kinds of movements. Further, all patients were female."^[2, p.822-23]

Rett published the first paper about the impairment, describing it as a degenerative brain disease, in the Austrian medical newsletter, *Wiener Medizinische Wochenschrift* in 1966, but experienced little attention among his colleagues. Realising the limitations of publishing in German, the physician wrote an English paper which appeared in 1977 in the *Handbook of Clinical Neurology*. Furthermore, he edited a film and presented it at various meetings throughout Europe^[2]. Yet, wide interest in RTT was only raised in 1983 through an article by Bengt Hagberg, Jean Aicardi and Karin Dias. Hagberg, a Swedish paediatrician, had watched several girls with the characteristic hand stereotypies between 1960 and 1980 and had presented his observations at a board meeting of the European Federation of Child Neurology Societies in 1981. Shortly after the meeting, 35 girls with similar symptoms had been identified in Sweden, France and Portugal^[5].

During his research, Bengt Hagberg discovered Rett's first description of the disease and met him in Toronto in fall 1981. Both physicians were convinced that there was a great need for multinational discussions about the condition and organised an informal workshop in Vienna in April 1982^[5]. Among the participants of this first informal meeting was a research team from Japan, who had already described the impairment in 1978^[6]. Further workshops followed in Vienna and in 1985 the first international symposium on RTT was held in Baltimore^[5].

By organising these meetings, Hagberg and Rett made the first important step towards widespread recognition of the disease and the formation of international research groups.

1.1.2 Definition of the diagnostic criteria

As there were no laboratory tests for accurate diagnosis of RTT, the attending scientists of the 2nd Rett Syndrome Conference in Vienna in 1984 recognised the need of cataloguing the main symptoms, in order to provide a clinically applicable tool for physicians to

correctly diagnose patients with RTT. Therefore they defined the first guidelines of diagnostic criteria for RTT, which were published in the journal *Brain and Development* in 1985 (Table 1.1)^[41].

Criteria for inclusion
1. Female sex
2. A normal pre- and perinatal period; essentially normal psychomotor development through the first 6 months, often 12-18 months of life
3. Normal head circumference at birth
4. Early behavioural, social and psychomotor regression (loss of achieved abilities); development of communication dysfunction and signs of dementia
5. Loss of acquired purposeful had skills through ages 1-4 years
6. Hand wringing-clapping-"washing" hand stereotypies appearing between ages 1 and 4 years
7. Appearance of gait apraxia and truncal apraxia/ataxia through ages 1-4 years
8. Diagnosis tentative until 3-5 years of age
Criteria for exclusion
1. Visceromegaly, other signs of organ storage
2. Retinopathy or optic atrophy before age of 6 years
3. Congenital microcephaly
4. Perinatally acquired brain impairment

Table 1.1: Diagnostic criteria for Rett Syndrome 1985^[41].

Considering the possibility of undiagnosed male cases, the diagnostic criteria were revised in 1988 by the Rett Syndrome Diagnostic Criteria Work Group, removing the restriction to females. Furthermore the criterion of ‘normal psychomotor development through the first 6 months’ was questioned by some scientists and studies' results gave reasonable doubt to that hypothesis. The revised diagnostic criteria therefore stated an ‘apparently normal psychomotor development through the first 6 months’ as criterion for inclusion^[8].

Supportive criteria were added due to various articles that revealed a number of additional complications in several patients with RTT. This should facilitate diagnosis in general clinics and hospitals, which are normally the first contact points of the patients^[8].

The advances in the research of neurobiology and genetics of RTT as well as the increasing recognition of atypical presentations of the disease led to discontent of scientists and physicians with the current diagnostic criteria, judging them as too restrictive. Therefore a group of specialists revised the criteria during the European Paediatric Neurology Society Meeting in Baden Baden in 2001. Their attempt was to create a practical diagnostic tool for primary care providers which was "as simple as possible"^[7, p.293], yet sufficiently extensive

to include atypical or borderline variants of the impairment^[7].

Though genetic research had led to the discovery of the *MECP2* gene as the molecular cause of the disease, a verified mutation in the gene was not listed as an inclusion criterion as up to 5% of patients with classic Rett are mutation-negative. Furthermore, *MECP2* mutations were found in people without RTT-like symptoms. Therefore the diagnosis of RTT was - and still remains - primarily clinical^[7].

The latest revision of the diagnostic criteria occurred in 2010 with the aim to further simplify diagnosis of both classic and atypical RTT patients^[9].

1.1.3 Discovery of the genetic background

Due to its restriction to females, Hagberg - in his first article describing RTT - already linked the disease to a dominant mutation on one X chromosome, resulting in affected girls and non-viable males^[10]. A few years later first cases of boys with signs of RTT were reported. Still, Hagberg's opinion of RTT being an X-linked dominant, male-lethal (XDML) disease was shared by leading scientists as the reported males were affected by Klinefelter Syndrome and therefore had an protective second X chromosome^[10].

A XDML disease normally causes an unequal sex ratio within affected families with an increase in spontaneous abortion of male foetuses. Yet, data analyses of families with RTT showed no alteration of sex ratio or increase of miscarriages^[11]. This situation, together with the fact that girls with RTT usually had healthy parents, led scientists to believe that each case derived from a de novo mutation. Findings of rare family cases of RTT and the concordance of monozygotic female twins for the disorder were ascribed to germinal mosaicism in one of the parents or to a inheritance from a mutation-carrier mother^[10]. In some families with RTT, boys with severe neonatal encephalopathy were described^[12].

Cytogenetic analysis conducted by Wahlström in 1985 showed a fragile site on chromosome Xp22 in several girls with RTT^[13], yet later investigations revealed that Xp22 was a common fragile site in normal populations and could therefore not be used as a chromosomal marker for RTT^[14].

A major breakthrough occurred in 1999 when a team of scientists of the Baylor College detected mutations at the *MECP2* gene, located at Xp28, in some of their study participants^[15]. This gene encodes for the methyl-CpG-binding protein 2 (MeCP2) which consists of two functional domains: The methyl-binding-domain (MBD), which specifically binds to DNA at methylated CpG dinucleotides, and the transcription repressor

domain (TRD) that, in interaction with other proteins, leads to transcriptional repression^[16]. Amir and colleagues found six different mutations in almost 25% of the 21 sporadic cases and in one of eight familial cases with classic Rett. The mutation positive family consisted of two half sisters carrying the same mutation at the methyl-CpG-binding domain (MBD) of the protein. As their mother was healthy and had random X-inactivation pattern, she was supposed to have a germline mosaicism^[15].

By 2003 a number of 218 different *MECP2* mutations, distributed along the whole gene, had been described with an overall detection rate of 61,7% of all patients with RTT^[17]. Seventy-five percent of sporadic cases and 29% of familial cases had been reported as mutation-positive^[18]. The mutations include all types and lead to a variety of phenotypes including classic RTT as well as atypical variants. Subsequent screening showed that the eight most common missense and nonsense mutations account for about 70% of all mutations (Figure 1.2)^[19].

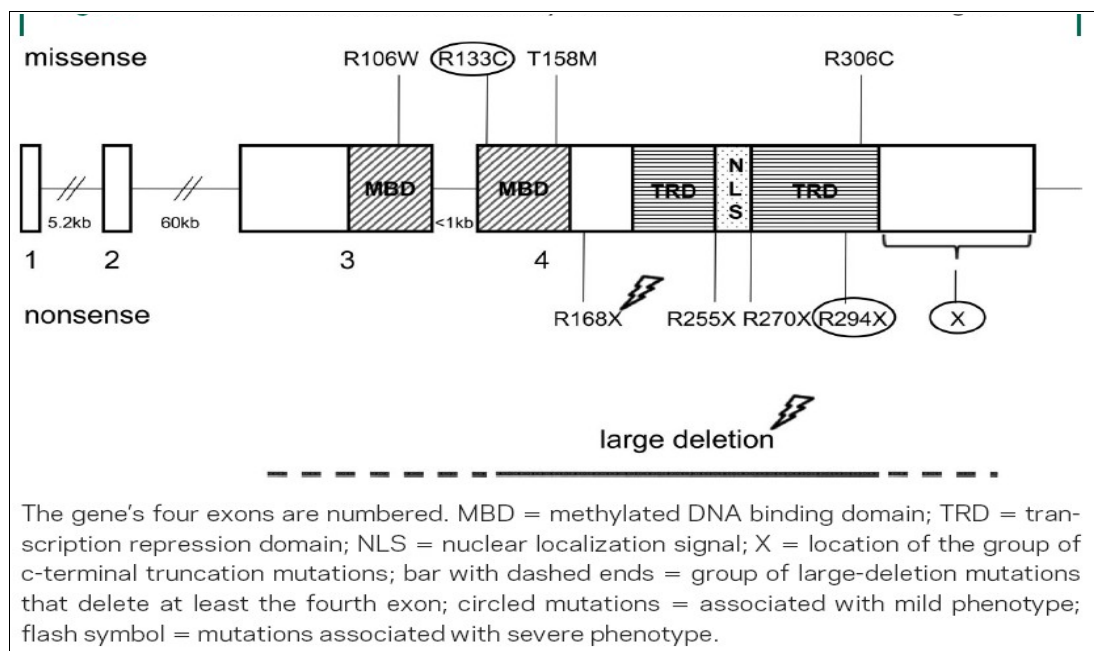


Figure 1.2: Location of the eight most common mutations of *MECP2* including a description about their phenotypic outcome^[40].

The first *MECP2* mutations in males were found in infants with severe neonatal encephalopathy, who mostly died within the first 2 years of life. Until 2003, all these cases had a relative with RTT or a brother with neonatal encephalopathy^[20-23]. Lynch and colleagues described the first sporadic case of a boy with this disease in 2003^[24].

Two boys with *MECP2* mutations and cognitive impairment were found in 2000, yet later

studies showed that *MECP2* mutations are only a rare cause of cognitive impairment in males^[25,26].

Two further genes that were associated with variants of RTT were discovered over the years. Mutations in the *CDKL5* gene was described to lead to a variant with early onset of severe seizures, the so-called Hanefeld Variant^[27]. The other gene, *FOXG1*, was identified to be responsible for the Congenital Variant of RTT^[28].

Soon after the discovery of *MECP2* mutations in RTT, scientists started to perform genotype-phenotype correlations studies. Yet the results have been controversial, which was ascribed to the fact that different severity scales were used to describe the phenotypes and that *MECP2* is subject to X-chromosome inactivation which could lead to milder phenotypes by favourable inactivation patterns^[29,30].

Additionally, mutations in the *MECP2* gene were found to be present in a wider range of different diseases such as autism, Angelman Syndrome, nonspecific cognitive impairment and systemic lupus erythematosus^[31,32].

Summarising, the discovery of *MECP2* mutations in most cases of classic RTT was a important milestone for further research in pathophysiology and therapeutic approaches, yet the clinical picture of RTT and its variants is still the most important feature for diagnosis.

1.1.4 Formation of family and research organisations

Soon after worldwide recognition of the disease, the first family organisation for RTT was initiated by Kathy Hunter, US-American mother of a girl with RTT, who was misdiagnosed with autism until her early adolescence^[33]. Hunter intended to raise awareness about the impairment in the society, give support to affected families and fund research for treatments and a cure of the syndrome. She therefore started the International Rett Syndrome Association (IRSA) in 1984. By 1995 the organisation had several local offices around the world, providing information, activities and meetings for families with RTT. Furthermore 12 million dollars had been invested in research groups to identify the cause of the disease and find a treatment^[34].

Four years later, the association's funding of a group of scientists at the Baylor College of Medicine led to the discovery of *MECP2* as cause of RTT^[15,35].

After the finding of MECP mutations in girls with RTT in 1999, a small group of parents initialised the Rett Syndrome Research Foundation (RSRF), which - contrary to the IRSA -

should emphasise on the scientific exploration of RTT. Co-founder and scientific director Monica Coenraads put an effort to organise conferences and seminars and bring scientists from various disciplines to work on RTT. A great success for the foundation occurred in 2007, when Adrian Bird, chairman of the RSRF's scientific advisory board, successfully reversed the symptoms in a mouse model^[36].

In June 2007, the two big organisations - the IRSA and the RSRF - merged to become the International Rett Syndrome Foundation (IRSF), which is still the most important foundation for research and support for families^[35]. Various countries have local RTT associations and websites but most of them are part of the international network. Some families maintain their own foundations but none of them ever achieved the recognition of the IRSF.

Yet, some parents and scientists were determined to maintain the focus on scientific research and therefore established the Rett Syndrome Research Trust (RSRT) in September 2008. Again, Monica Coenraads was one of the founders of the organisation and has been executive director since then. With well-known scientists, e.g. Adrian Bird and Huda Zoghbi, in the leadership, the RSRT has its focus on understanding the function of MeCP2 in the brain, finding possibilities to increase the levels of the MeCP2 protein and testing therapies to alleviate the symptoms of RTT^[36,37]. A team of scientists from the University of Virginia was funded by the RSRT to study the role of microglia cells in RTT^[38]. In 2012 they revealed that bone marrow transplant could reverse some of the symptoms in *Mecp2* null mice, which brings hope to families affected by this severe disorder^[39].

References for 1.1 History of RTT

- [39] Tragl KH. Chronik der Wiener Krankenanstalten. Vienna: Böhlau Verlag; 2007. p.563
- [40] Haas RH. Andreas Rett. In: Ashwal S, editor. The Founders of Child Neurology. San Francisco: Norman Publishing; 1990. p.822-23.
- [41] International Rett Syndrome Foundation. About Rett Syndrome - History. <http://www.rett Syndrome.org/content/blogcategory/13/969>; accessed March 25th, 2012.
- [42] Wikipedia - The free encyclopaedia. Andreas Rett. http://en.wikipedia.org/wiki/Andreas_Rett; accessed May 30th, 2012.
- [43] Hagberg B. Clinical manifestations and stages of Rett syndrome. Ment Retard Dev Disabil Res Rev 2002;8(2):61-5.
- [44] Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. Rett disorder and the developing brain. Oxford: Oxford University Press; 2001. p.1-26.
- [45] Hagberg B, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. Eur J Paediatr Neurol 2002;6(5):293-7.
- [46] Trevathan E, chairperson. Diagnostic criteria for Rett syndrome. The Rett Syndrome Diagnostic Criteria Work Group. Ann Neurol 1988;23(4):425-8.
- [47] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol 2010;68(6):944-50.
- [48] Clarke A, Schanen C, Anvret M. Towards the genetic basis of Rett syndrome. In: Kerr AM, Witt Engerström I, editors. Rett disorder and the developing brain. Oxford: Oxford University Press; 2001. p.27-55.

- [49] Comings DE. The genetics of Rett syndrome: the consequences of a disorder where every case is a new mutation. *Am J Med Genet Suppl* 1986;1:383-8.
- [50] Schüle B, Armstrong DD, Vogel H, Oviedo A, Francke U. Severe congenital encephalopathy caused by MECP2 null mutations in males: central hypoxia and reduced neuronal dendritic structure. *Clin Genet* 2008;74(2):116-26.
- [51] Wahlström J. Genetic implications of Rett syndrome. *Brain Dev* 1985;7(6):573-4.
- [52] Moore JW, Tuck-Muller CM, Murphy M, Naidu S, Thomas GH. Chromosome studies in 10 patients with the Rett syndrome. *Am J Med Genet Suppl* 1986;1:345-54.
- [53] Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;23(2):185-8.
- [54] Meehan RR, Lewis JD, Bird AP. Characterization of MeCP2, a vertebrate DNA binding protein with affinity for methylated DNA. *Nucleic Acids Res* 1992;20(19):5085-92.
- [55] Miltenberger-Miltenyi G, Laccone F. Mutations and polymorphisms in the human methyl-CpG-binding protein MECP2. *Hum Mutat* 2003;22(2):107-15.
- [56] Amir RE, Van den Veyver IB, Schultz R, Malicki DM, Tran CQ, Dahle EJ, et al. Influence of mutation type and X chromosome inactivation on Rett syndrome phenotypes. *Ann Neurol* 2000;47(5):670-9.
- [57] Williamson SL, Christodoulou J. Rett syndrome: new clinical and molecular insights. *Eur J Hum Genet* 2006;14(8):896-903.
- [58] Villard L, Kpebe A, Cardoso C, Chelly PJ, Tardieu PM, Fontes M. Two affected boys in a Rett syndrome family: clinical and molecular findings. *Neurology* 2000;55(8):1188-93.
- [59] Hoffbuhr K, Devaney JM, LaFleur B, Sirianni N, Scacheri C, Giron J, et al. MECP2 mutations in children with and without the phenotype of Rett syndrome. *Neurology* 2001;56(11):1486-95.
- [60] Geerdink N, Rotteveel JJ, Lammens M, Sistermans EA, Heikens GT, Gabreëls FJ, et al. MECP2 mutation in a boy with severe neonatal encephalopathy: clinical, neuropathological and molecular findings. *Neuropediatrics* 2002;33(1):33-6.
- [61] Zeev BB, Yaron Y, Schanen NC, Wolf H, Brandt N, Ginot N, et al. Rett syndrome: clinical manifestations in males with MECP2 mutations. *J Child Neurol* 2002;17(1):20-4.
- [62] Lynch SA, Whatley SD, Ramesh V, Sinha S, Ravine D. Sporadic case of fatal encephalopathy with neonatal onset associated with a T158M missense mutation in MECP2. *Arch Dis Child Fetal Neonatal Ed* 2003;88(3):F250-2.
- [63] Meloni I, Bruttini M, Longo I, Mari F, Rizzolio F, D'Adamo P, et al. A mutation in the rett syndrome gene, MECP2, causes X-linked mental retardation and progressive spasticity in males. *Am J Hum Genet* 2000;67(4):982-5.
- [64] Santos M, Temudo T, Kay T, Carrilho I, Medeira A, Cabral H, et al. Mutations in the MECP2 gene are not a major cause of Rett syndrome-like or related neurodevelopmental phenotype in male patients. *J Child Neurol* 2009;24(1):49-55.
- [65] Weaving LS, Christodoulou J, Williamson SL, Friend KL, McKenzie OL, Archer H, et al. Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. *Am J Hum Genet* 2004;75(6):1079-93.
- [66] Ariani F, Hayek G, Rondinella D, Artuso R, Mencarelli MA, Spanhol-Rosseto A, et al. FOXP1 is responsible for the congenital variant of Rett syndrome. *Am J Hum Genet* 2008;83(1):89-93.
- [67] Halbach NS, Smeets EE, van den Braak N, van Roozendaal KE, Blok RM, Schrandt-Stumpel CT, et al. Genotype-phenotype relationships as prognosticators in Rett syndrome should be handled with care in clinical practice. *Am J Med Genet A* 2012;158A(2):340-50.
- [68] Amir RE, Zoghbi HY. Rett syndrome: methyl-CpG-binding protein 2 mutations and phenotype-genotype correlations. *Am J Med Genet* 2000;97(2):147-52.
- [69] Sanmann JN, Schaefer GB, Buehler BA, Sanger WG. Algorithmic approach for methyl-CpG-binding protein 2 (MECP2) gene testing in patients with neurodevelopmental disabilities. *J Child Neurol* 2012;27(3):346-54.
- [70] Webb R, Wren JD, Jeffries M, Kelly JA, Kaufman KM, Tang Y, et al. Variants within MECP2, a key transcription regulator, are associated with increased susceptibility to lupus and differential gene expression in patients with systemic lupus erythematosus. *Arthritis Rheum* 2009;60(4):1076-84.
- [71] Sams R. Health care pioneers - Kathy Hunter. *Baltimore Business Journal* 15 Sep 2003; <http://www.bizjournals.com>, accessed April 15th, 2012.
- [72] Koerber J. A circle of help: the International Rett Syndrome Association gives parents a shoulder to lean on. *The Exceptional Parent*. http://www.findarticles.com/p/articles/mi_go2827/is_n1_v25/ai_n28651519/, accessed April 15th, 2012.
- [73] International Rett Syndrome Foundation. About IRSF - History. http://www.rettssyndrome.org/index.php?option=com_content&task=view&id=21&Itemid=816, accessed April 15th, 2012.
- [74] Rett Syndrome Research Trust. About RSRT. <http://www.rsrt.org/about-rsrt>, accessed March 18th, 2012.
- [75] Rett Syndrome Research Trust. Research - Our Projects. <http://www.rsrt.org/research/our-projects>, accessed April 18th, 2012.
- [76] Rett Syndrome Research Trust. Bone Marrow Transplant arrests symptoms in model of Rett Syndrome. <http://www.rsrt.org/about-rsrt/press-releases/bone-marrow-transplant-arrests-symptoms-in-model-of-rett-syndrome>, accessed April 18th, 2012.
- [77] Derecki NC, Cronk JC, Lu Z, Xu E, Abbott SB, Guyenet PG, Kipnis J. Wild type microglia arrest pathology in a

- mouse model of Rett syndrome. *Nature* 2012;484(7392):105-9.
- [78] Zhang Y, Minassian BA. Will my Rett syndrome patient walk, talk, and use her hands? *Neurology* 2008;70(16):1302-3.
- [79] Hagberg B, Goutières F, Hanefeld F, Rett A, Wilson J. Rett syndrome: criteria for inclusion and exclusion. *Brain Dev* 1985;7(3):372-3.

1.2 Clinical symptomatology

1.2.1 Diagnostic criteria for RTT

A catalogue of diagnostic criteria for RTT was first published in 1985 by Hagberg and colleagues^[1]. Despite the discovery of mutations in the *MECP2* gene as underlying cause of the disease in 1999^[2], the criteria for inclusion have ever since been based exclusively on the patients' clinical presentation^[3-5]. The presence of *MECP2* mutations has not been incorporated in the list of inclusion criteria because even extensive genetic testing has failed to reveal a mutation in up to 5% of individuals with the typical phenotype of classic RTT. Additionally, *MECP2* mutations have been found in people without clinical features of the disease^[4-8].

The diagnostic criteria for RTT have continuously been revised in order to correspond to the latest findings of scientific research^[3-5]. As cases of males with classic RTT have been found, the initial restriction to females was removed from the list of necessary criteria^[3]. Furthermore, the discovery of subtle abnormalities mingling with signs of normal psychomotor development (such as achievement of developmental milestones) led to a withdrawal of 'normal psychomotor development through the first 6 months' as required criterion for inclusion. Instead, 'grossly abnormal psychomotor development in first 6 months of life' was listed as criterion for exclusion^[5].

However, some criteria for inclusion have been left unchanged ever since the first edition of the diagnostic criteria: Loss of acquired purposeful hand skills, gait abnormalities and the development of stereotypic hand movements^[1,3-5].

The latest revision of the diagnostic criteria was issued in 2010 by Neul and colleagues (Table 1.2)^[5]. Their main intent was to "clarify and simplify the diagnosis of typical, or classic, RTT"^[5, p.945]. Thus, the requirements for inclusion were limited to four main criteria in addition to the presence of regression. Neul and colleagues further stressed the absolute necessity of "a period of regression followed by recovery or stabilisation"^[5, p.947] for the diagnosis of atypical RTT in order to delineate it from degenerative disorders. The researchers also summarised the clinical features and the genetic background of the three

main variant forms of RTT (see Table 1.7 in Chapter 1.2.4 Specific variants of RTT)^[5].

RTT Diagnostic Criteria 2010	
Consider diagnosis when postnatal deceleration of head growth observed.	
Required for typical or classic RTT	
1	A period of regression followed by recovery or stabilization*
2	All main criteria and all exclusion criteria
3	Supportive criteria are not required, although often present in typical RTT
Required for atypical or variant RTT	
1	A period of regression followed by recovery or stabilization*
2	At least 2 out of the 4 main criteria
3	5 out of 11 supportive criteria
Main Criteria	
1	Partial or complete loss of acquired purposeful hand skills.
2	Partial or complete loss of acquired spoken language**
3	Gait abnormalities: Impaired (dyspraxic) or absence of ability.
4	Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
Exclusion Criteria for typical RTT	
1	Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems***
2	Grossly abnormal psychomotor development in first 6 months of life [#]
Supportive Criteria for atypical RTT^{##}	
1	Breathing disturbances when awake
2	Bruxism when awake
3	Impaired sleep pattern
4	Abnormal muscle tone
5	Peripheral vasomotor disturbances
6	Scoliosis/kyphosis
7	Growth retardation
8	Small cold hands and feet
9	Inappropriate laughing/screaming spells
10	Diminished response to pain
11	Intense eye communication - "eye pointing"
[†] Because <i>MECP2</i> mutations are now identified in some individuals prior to any clear evidence of regression, the diagnosis of "possible" RTT should be given to those individuals under 3 years old who have not lost any skills but otherwise have clinical features suggestive of RTT. These individuals should be reassessed every 6–12 months for evidence of regression. If regression manifests, the diagnosis should then be changed to definite RTT. However, if the child does not show any evidence of regression by 5 years, the diagnosis of RTT should be questioned. ^{**} Loss of acquired language is based on best acquired spoken language skill, not strictly on the acquisition of distinct words or higher language skills. Thus, an individual who had learned to babble but then loses this ability is considered to have a loss of acquired language. ^{***} There should be clear evidence (neurological or ophthalmological examination and MRI/CT) that the presumed insult directly resulted in neurological dysfunction. [#] Grossly abnormal to the point that normal milestones (acquiring head control, swallowing, developing social smile) are not met. Mild generalized hypotonia or other previously reported subtle developmental alterations¹⁶ during the first six months of life is common in RTT and do not constitute an exclusionary criterion. ^{##} If an individual has or ever had a clinical feature listed it is counted as a supportive criterion. Many of these features have an age dependency, manifesting and becoming more predominant at certain ages. Therefore, the diagnosis of atypical RTT may be easier for older individuals than for younger. In the case of a younger individual (under 5 years old) who has a period of regression and ≥ 2 main criteria but does not fulfill the requirement of 5/11 supportive criteria, the diagnosis of "probably atypical RTT" may be given. Individuals who fall into this category should be reassessed as they age and the diagnosis revised accordingly.	

Table 1.2: Latest revision of the diagnostic criteria for RTT^[5].

References for 1.2.1 Diagnostic criteria for RTT

- [1] Hagberg B, Goutières F, Hanefeld F, Rett A, Wilson J. Rett syndrome: criteria for inclusion and exclusion. *Brain Dev.* 1985;7(3):372-3.
- [2] Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;23(2):185-8.
- [3] Trevathan E, chairperson. Diagnostic criteria for Rett syndrome. The Rett Syndrome Diagnostic Criteria Work Group. *Ann Neurol* 1988;23(4):425-8.
- [4] Hagberg B, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. *Eur J Paediatr Neurol* 2002;6(5):293-7.
- [5] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;68(6):944-50.
- [6] Temudo T, Santos M, Ramos E, Dias K, Vieira JP, Moreira A, et al. Rett syndrome with and without detected MECP2 mutations: an attempt to redefine phenotypes. *Brain Dev* 2011;33(1):69-76.
- [7] Sanmann JN, Schaefer GB, Buehler BA, Sanger WG. Algorithmic approach for methyl-CpG-binding protein 2 (MECP2) gene testing in patients with neurodevelopmental disabilities. *J Child Neurol* 2012;27(3):346-54.
- [8] Webb R, Wren JD, Jeffries M, Kelly JA, Kaufman KM, Tang Y, et al. Variants within MECP2, a key transcription regulator, are associated with increased susceptibility to lupus and differential gene expression in patients with systemic lupus erythematosus. *Arthritis Rheum* 2009;60(4):1076-84.

1.2.2 Clinical stages of classic RTT

A model of four stages to describe the clinical course of classic RTT was developed by Witt Engerström and Hagberg in 1986^[1]. Stage I was stated to have an onset between 6 and 18 months of age and a duration of weeks to months. During this period the infants show some developmental progress and mostly pass clinical screening tests, though subtle signs of developmental stagnation are already present^[1,2]. Between the age of 1 to 4 years, a delay in the achievement of motor milestones becomes obvious and acquired skills are often lost. Furthermore autistic features are commonly seen^[3]. This period, called stage II, can last for weeks or months and is followed by the pseudo-stationary stage (stage III) between preschool and school age. Autistic features improve and some girls are able to recover lost skills. However, breathing abnormalities, seizures, dystonia and unsteady gait are prominent in this stage^[4]. Finally muscle hypertonia and scoliosis lead to reduced mobility and wheelchair dependency in adulthood. This period, called stage IV, can last for decades^[3].

Due to growing evidence of developmental deviation already within the first 6 months of life, the model was adapted by Naidu, who corrected the age of onset of stage I between perinatal period and 18 months^[5].

Table 1.3 shows the clinical features and differential diagnosis of the four different stages of RTT.

Stage and Age	Clinical Features	Differential Diagnosis
1: Perinatal period to 18 mo	Deceleration of head growth Disinterest in environment Hypotonia	Benign congenital hypotonia Prader-Willi Syndrome Cerebral palsy
2: 1-3 yr	Loss of expressive language Developmental regression Weight loss Poor hand use Seizures Abnormal EEG background and spikes Insomnia and irritability	Autism Psychosis Epileptic encephalopathy Neurodegenerative disease Late infantile neuronal-ceroid lipofuscinosis
3: 2-10 yr	Severe cognitive impairment Seizure Hand wringing, tapping or mouthing Respiratory irregularities tremulousness Growth retardation	Spinocerebellar degeneration Angelman Syndrome Ataxic cerebral palsy
4: >10 yr	Progressive scoliosis Distal muscle wasting Trophic disturbance Decreasing mobility Improved social interaction Seizures Respiratory abnormalities	Neurodegenerative disease of unknown cause

Table 1.3: Clinical characteristics and differential diagnoses of RTT by stage of illness[5].

Though this four-stage-model can still be found in literature, a more commonly used description of the clinical course is based on the British survey and is divided into three periods: 1) pre-regression, 2) regression and 3) post-regression^[1].

1.2.2.1 The pre-regression period (stage I)

Early diagnostic criteria for RTT included an apparently normal psychomotor development of the patients within the first 6 to 18 months of life, followed by a period of developmental stagnation and partial or total loss of acquired skills^[6].

However retrospective analyses of infant screening records and questioning of parents revealed that signs of abnormal behaviour and development are already present during early infancy^[8,10,11,13]. Evaluation of newborn records showed that girls with RTT had lower birth weights and lower head circumferences than healthy children^[7,8]. Yet, alterations of somatic growth were not found in a study of newborn *Mecp2*-null mice^[9].

Parental questionnaires revealed that almost 40% of infants with RTT demonstrated difficulties - predominantly in feeding - during the first week of life and about 15% needed special nursery and help breathing. Parents' recall of the first 6 months often described a very placid and quiet baby, who was 'easily satisfied' and had 'no acknowledgement of the

world around her'. Furthermore many girls were regarded as floppy, suggesting hypotonia (Table 1.4)^[7]. Longitudinal data from the British Rett survey showed that 80% of the girls were hypotonic before regression^[1].

Code: Placid 'Unusually passive—happy always! Never crying not even when hungry—or when had chicken pox at 6 months' 'Was very placid and slept a lot compared to friends babies' 'She was always 'too good' a baby. Very placid, fed well (breast fed)' 'Over placid. Did not cry much' 'She was 'too good'. Extremely placid with no acknowledgement of the world around her' 'Extremely placid, very good sleeper' 'Very placid, easily satisfied' 'Low tone, slow to smile, very placid, sleepy' 'She was a placid baby with a voracious appetite and a good feeder' Code: Floppy 'Poor feeder. Very floppy. Cried a lot' 'She was floppy compared to other children' 'Until 6 months was unable to support her own head—hypotonic—floppy' 'She always seemed to have a very floppy tone compared with my first child and did not seem to be making her milestones' 'Her doctor as the time classed her as a 'floppy baby'' '**** was a very 'floppy' baby—however in the first 6 months we just saw this as her being a very cuddly baby' 'Kind of 'floppy' tone' 'Lots of reflux, otherwise a very content 'floppy' baby' 'She was a little floppy/soft'
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Table 1.4: Examples of parental expressions about unusual behaviours of their child during the first 6 months of life in a retrospective study by Leonard et al^[7].

Parents also commonly stated that the girls were good sleepers and slept longer during daytime. In the normal development of infants, the sleep-wake-rhythm follows a ultradian pattern within the first month but is then adjusted and by 4 months of age the infants should achieve a circadian rhythm with modulated sleep periods over the day. The parents' statements lead to believe, that this development is altered in girls with RTT^[10].

Between 6 and 10 months of life parents' main concern was related to their daughter's motor development^[7]. Some infants were reported to have a delay in head control and one third was told to be unable to roll over on time. A delay in sitting was mentioned by almost one third of the parents^[11]. Of 311 cases analysed by Leonard and colleagues through parental inquiries, only 20% were able to crawl by 10 months. Twenty percent would not move around at all whereas the remaining were either rolling, commando crawling or bottom shuffling^[7]. Though 2% of the study participants could walk independently by 10 months - which is early compared to normally developing children - other researchers found a delay in standing and walking^[11]. In a Swedish study, Witt Engerström described that more than half of the girls would not stand by 1 year. Furthermore she mentioned "excessive bilateral hand movements"^[1, p.5] already in infancy^[1]. Segawa also found

abnormalities in the development of skilful hand movements from mid infancy on. Though 18 out of 19 patients could bring both hands to the midline, transfer of an object from one hand to the other was either delayed or impossible. Furthermore more than a half of the patients were unable to perform reaching or pincer grasps^[11]. A delay in the development in motor coordination was later also found in studies of *Mecp2*-null mice^[9,12].

In total, parental inquiries revealed that more than 80% of the parents retrospectively suspected abnormalities in their daughter's development or behaviour within the first 10 months of life and almost 60% already before 6 months of age^[7,13].

Though parental questionnaires and medical records are an important tool to study the early development of RTT patients, one needs to consider that parents' memories might be biased and medical records could be incomplete. Therefore, retrospective analyses of home videos are increasingly used for research in this field. These videos were recorded by parents for their family archive prior to their daughter's diagnoses. The strength of this method is that the development and behaviour of the infant can be meticulously observed and that it is independent from parents' recall. Still, one needs to consider that the infant was not constantly recorded. Thus, the absence of a feature or movement does not mean that it was not performed by the child^[14].

Retrospective analyses of home videos have confirmed that early developmental and behavioural abnormalities are present already after birth^[15,17,19,21,23]. Einspieler and colleagues studied the performance of general movements in 14 girls with classic RTT^[15]. These spontaneous movements normally arise around 9-10 weeks postmenstrual age and can be seen until 5 months postterm. They are divided into two age-specific categories: Writhing movements can be observed until the end of the 2nd month of life. They involve the whole body with a variability in speed, intensity and force. During the 3rd month postterm the movement pattern changes and fidgety movements arise. "Fidgety movements are continual small movements of small moderate speed, and variable acceleration of neck, trunk, and limbs in all directions"^[15, p.9]. Infants with brain damage have been mentioned to show abnormal general movements with less variability and elegance and at times monotonous character^[15,16]. "An absence of fidgety movements has been shown to predict the spastic and dyskinetic forms of cerebral palsy"^[15, p.12]. The video study revealed that none of the 14 girls had normal general movements. Writhing movements mostly consisted of poor repertoire with a monotonous character and lack of complexity. Some girls showed jerky and fast movements while others moved abnormally slow. The performance of

fidgety movements was either "jerky and too slow or jerky, abrupt and disorganised"^[15, p.11]. In four cases, fidgety movements were absent at all. However, the abnormal general movements of these girls did not follow a specific pattern and were different to those found in infants with brain lesion.

Other abnormal movements, especially regarding the hand and the face, were found in video studies by different researchers^[17-19]. Stereotypic hand movements were described by Einspieler and colleagues from 3 months onwards. "They consisted of unilateral or bilateral 1) repetitive pronation of the hand with simultaneous dorsiflexion of the wrist; 2) excessive repetitive opening and closing of both hands, sometimes even with synchronised plantar flexion of all the toes; or 3) repeated brining of the palmar sides of both hands together (like praying), raising both hands and separating them again"^[18, p.698]. Temudo and colleagues also found washing-like movements, repetitive hand-to-mouth movements and abnormally twisted fingers in their case study^[17]. Furthermore, some girls did not show adequate age-related motor patterns^[17,18]. In a study by Burford and colleagues, midwives who were blinded to the girls' clinical status and had no prior knowledge of the disease, commonly stated concern about the infants' hand movements or positions already within the first 10 days of life^[19].

Regarding the face, abnormal and repetitive protrusion of the tongue and asymmetric opening or closing of the eyelid after or during a blink could frequently be observed^[18]. Furthermore Einspieler and colleagues described that "only after repeated frame-by-frame analysis did it become clear that eight girls had bursts of abnormal facial expressions.[...]. At 5 and 6 months, one third of the cases had a frozen, bizarre, and inadequate smile"^[18, p.698] (Table 1.5). Abnormal postures of the limbs during sitting, sleeping^[18] and crawling^[17] have been described. A slumped body posture suggesting hypotonia was rarely observed by Einspieler and colleagues, whereas half of their patients rather showed a stiff body posture^[18]. This contradicts earlier findings from parental questionnaires^[1,7].

Age	Abnormal general movements	Postural stiffness or slumped posture	Asymmetric eye opening and closing	Tongue protrusion	Bizarre smile	Bursts of abnormal facial expression
Birth until 2 mo	10	8	5	8	2	2
3-4 mo	4	3	3	2	—	3
5-6 mo	2	2	2	3	4	3

Table 1.5: First appearance (number of infants per 2-mo epochs) of abnormal signs observed in 22 participants in a study by Einspieler et al^[18].

As partial or total loss of acquired speech is one of the diagnostic criteria for RTT^[20], home videos were also used to analyse the development of vocalisation^[21-23]. In a study with six females with Preserved Speech Variant between 7 to 24 months of age, Marschik and colleagues found that sequences of normal vocalisation were intermittent with atypical features. The "atypical vocalizations [consisted] of inhalatory, pressed or high-pitched crying-like character"^[21, p.453]. While abnormal inspiratory vocalisations were only found during the first year of life, pressed and high-pitched crying-like vocalisations increased and were observed in all study participants during the 2nd year. Furthermore simultaneous occurrence of hand stereotypies and abnormal vocalisations was found during the 2nd year of life. Overall, "complex consonant-vowel clusters were rare"^[21, p.454] and echolalia of meaningless vocalisation became prominent during the 2nd year.^[21] Only one out of six girls uttered canonical babbling on time and "she was the only one to produce word combinations before the onset of regression"^[21, p.454]. This corresponds to findings of a Swedish survey, where only one out of 20 girls was able to produce a three word sentence before regression^[1]. Studies on *Mecp2*-null mice showed that increased ultrasound vocalisations were the earliest sign of abnormal neonatal behaviour^[9].

Recordings of inspiratory vocalisation, intermittent vocalisation and apparently normal babbling of girls with RTT and recordings of healthy children were used to study recognition of vocalisation abnormalities among professionals and naive-listeners. Most of the professionals were able to correctly differentiate between normal and abnormal cooing vocalisations. The number of correct judgements increased in both groups for canonical babbling. More than 80% could give the right answer to the recordings of healthy infants, recordings of inhalatory vocalisation of girls with RTT as well as to the single intermittent sequence of an infant with RTT. Though more than 50 % stated the babbling sequence of a girl with RTT as inconspicuous, over 20% were indecisive and almost 20% suggested it as conspicuous^[22]. The latter example shows that even apparently normal vocalisations of infants with RTT raise some concern.

Another video study to analyse the recognition of early developmental deviation among non-professionals in the field, i.e. with no prior knowledge of the disease, was carried out by Burford and colleagues. Short sequences of both girls with RTT and normally developing infants were shown to midwives and health visitors. They were told to press a button if suspecting any developmental abnormalities. Furthermore they were given the opportunity to comment on their concerns. The group of girls with RTT received an almost

fivefold higher number of button presses than the group of healthy infants. This shows that health workers, even though they have no knowledge about Rett disorder, are able to detect signs of abnormal development in these infants. Yet, comparison of the comments and button presses within the RTT group "revealed fluctuations in the occurrence of early signs within individual infants and variability in their nature between infants"^[24, p.4], which most likely explains the difficulties in the early diagnosis of RTT^[19].

Though girls with RTT show developmental deviations already during infancy, most of them also reach important developmental milestones. Although some of them do this with delay, a few have been reported to achieve skills early compared to healthy children^[7,8,15]. Contrary to retrospective analyses of medical records and parental questionnaires^[11], a delay in head control could not be found in video analyses by Einspieler and colleagues^[18]. Fehr and colleagues revealed that 80% of the girls were able to sit on time and 50% could walk unassisted by 18 months. More than a half could speak at least one word before regression^[13]. Most of the girls achieve finger skills such as finger feeding and even on third of the girls in the Swedish survey performed pincer grasps^[1].

Thus, both signs of developmental deviation and normal development are present during early infancy in girls with RTT. As no specific pattern is followed and the girls show fluctuations in the occurrence of peculiarities, early diagnosis is still difficult. However, hope is given by studies, which showed that these deviations can be traced even by non-professionals when the girls are carefully observed^[19,22].

1.2.2.2 The regression period (stage II)

The regression period is one of the main characteristics of RTT and was, for a long time, believed to be the onset of the disease^[4]. It is the time, when parents recognise developmental and behavioural deviations in their child. Early diagnostic criteria described the onset of regression between 6 and 18 months of age, yet studies have shown that some cases reach this stage later in life^[1,6,13]. Therefore the latest revision of diagnostic criteria states regression as one of the main including criteria but without supposing a definite time of onset^[20]. The mean age of the beginning of this period has been found to be around the girls' 18th month of life^[1,13]. Some researchers revealed that the type and location of mutation and the degree of severity during the pre-regression period influences the age of onset^[4,13].

The period of regression is characterised by the loss of acquired skills, the development of

hand stereotypies and a change in the child's behaviour^[25] (Table 1.6). This features normally develop gradually, yet in some cases a rapid regression has been found after the girl has experienced some kind of stress^[26]. Fiumara and colleagues described a patient, who developed hand stereotypies and a major change in behaviour within 10 days after an infectious disease with high fever and a single generalised seizure^[27]. The behavioural change is often characterised by the appearance of autistic features; the girls begin to loose contact and interest in their environment, become agitated, irritable and frightened and develop episodes of unmotivated screaming or crying^[1,23,25,27,28]. Furthermore self abusive behaviour and disturbed night sleep with inappropriate night laughter has been observed^[1,6,29].

<i>Abnormal behavior</i>	<i>Positive (%)</i>	
Never uses finger pointing	14/16	(87.50)
Speech delay	16/16	(100.00)
Loss of verbal expression	8/11	(72.73)
Difficulty in copying movements made by other people	13/15	(86.67)
Autostimulation behavior	11/14	(78.57)
Extreme withdrawal	7/14	(50.00)
Dislikes being intervened while playing	2/12	(16.67)
No symbolic play	13/13	(100.00)
Insistence on sameness	6/12	(50.00)
Hyperactivity	4/12	(33.33)
Sudden laughing and crying without any apparent reason	11/15	(73.33)
Irregular and disturbed nocturnal sleep	6/14	(42.86)

Table 1.6: Behavioural abnormalities after the age of 1 year reported by parents in a retrospective study of 16 patients with RTT by Nomura and Segawa[36].

The loss of purposeful hand function mostly occurs around 18 to 27 months of age and affects the majority of the patients^[4,8,30]. Many of those who learn to feed themselves lose this ability during the regression period^[28]. Still, Huppke and colleagues revealed that a little more than 10% of their study participants were able to retain their hand function, though often with some deterioration^[8]. The onset of hand stereotypies mostly accompanies or follows, but rarely precedes, the loss of purposeful hand use^[31]. These stereotypies are defined as "involuntary, rhythmic, patterned, coordinated, repetitive and seemingly purposeless movements"^[31, p.1183]. They only appear during wakefulness and are mostly

characterised by washing-like or wringing movements of both hands. Other stereotypies such as bruxism, toe walking, trunk rocking and shifting weight might be present and can be seen especially when the hands are retained^[23,31,32]. Temudo and colleagues have described several cases which develop more than just one stereotypy^[31].

Apart from the loss of hand function and the appearance of hand stereotypies, loss of speech is another main diagnostic criteria for RTT^[20]. Most of the patients are able to babble and some use words before the onset of regression^[13]. Then language skills start to worsen and disappear at a mean age of 2 years^[8,23,30]. Only about 10% are able to retain some language skills, ranging from babbling to speaking more than 10 words^[8,33]. Some mutation types have been found to be related to a better retention of expressive language^[30].

Deterioration of gross motor skills is also present in most of the girl. Coordination of locomotion becomes impaired and sitting, standing and walking seems to get more difficult. Truncal ataxia, mostly of jerky type, appears between 1 and 4 years of age and leads to disequilibrium and unstable and abnormal gait^[1,6,25,28]. Sitting seems to be the best retainable gross motor skill, as Huppke and colleagues found that more than two thirds of their patients were still able to sit by the age of 5 years^[33]. Some researchers have described that about 20% of the girls who had learned to walk, lost this skill during regression and about another 20% developed major difficulties in walking^[28,32]. Though, evaluation of the clinical status of 123 girls with RTT at 5 years of age revealed that only 3% had stopped walking and 50% were still able to walk unsupported^[33]. This differences might be accounted for by the great variety of phenotypes of RTT.

Additionally to the loss of skills and the development of hand stereotypies, and especially towards the end of regression, some girls begin to develop epileptic seizures, scoliosis and breathing abnormalities - complications which are often associated with RTT^[1,34].

For the parents, the period of regression is one of the most difficult times to deal with. They perceive that something is wrong with their child, but often experience a lack of attention, support and knowledge from their clinicians. Many girls are primarily diagnosed with autism and some with cerebral palsy, developmental delay of unknown origin or general intellectual disability^[6,35]. Especially those born before the widespread recognition of RTT were commonly misdiagnosed until their adulthood^[25]. Furthermore, the age of diagnosis is influenced by the infrastructure and the quality of medical services in the country of residence as well as by socio-economic factors^[30,35]. Interrogating Chinese

families with daughters with RTT, Lim and colleagues found that most parents had encountered great difficulties during the diagnostic process due to lack of knowledge of their local clinicians and the absence of specialists on the field outside Peking. The researchers further stated: "Based on the incidence in Australia, we estimate about 1,000 girls would be born every year in China with Rett Syndrome, but to our knowledge, only approximately 200 cases have been identified to date."^[35, p.2] Fehr and colleagues revealed that better types of work and higher levels of education of the parents are associated with an earlier diagnosis of the child. In the same study, the researcher also found a correlation between the age when skills are lost or hand stereotypies arise and the age of diagnosis^[30]. In another study, Fehr and colleagues analysed the correlation between the achievement of developmental milestones and the age of diagnosis. The results showed that girls who were able to use words were diagnosed on average 6 months later than those who could only babble. Patients who had not learned to walk received the diagnosis on average 8 months earlier than those who had achieved this skill^[13]. Overall, the mean age of diagnosis in the study of Fehr and colleagues was 33 months. Considering that the mean age of regression onset is around the 18th month of live and generalising Fehr's findings about the age of diagnosis, the diagnostic process takes more than a year. Parents have commented that, even though getting the final diagnosis was devastating, it also brought relief. It reduced their emotional burden and uncertainty, enabled them to interact with other affected families and thus, prepare for the future^[29,35]. Finally, Witt Engerström and Kerr described that "regression was found to last for an average of 13 months, ending at a mean age of 30 months."^[1, p.7]

1.2.2.3 The post-regression period (stages III and IV)

By the age of 5 years, most of the girls have entered the post-regression period, which is characterised by a stabilisation of the disease. Autistic features diminish and the patients become more sociable. They get interested in interaction with their surroundings and seem to enjoy common activities^[1,26]. Though expressive language remains absent in most cases, the girls are able to communicate by intense eye contact and some can even express their needs through eye pointing^[3,26,32]. The developmental regression of motor abilities decelerates or even stagnates. A few patients manage to retrain lost skills or gain new abilities through occupational and physical therapies^[26,28,32]. In a Swedish study, Larsson and colleagues found that 18% of the girls were able to retrain gross motor functions such

as sitting, walking unassisted or walking up and down stairs and some even regained fine motor skills. Thirty-two percent of the study participants achieved to learn new skills after the regression period^[28].

Still, most of the patients are unable to use their hands purposefully and hand stereotypes remain prominent^[1,3,28]. Furthermore, the girls tend to develop a variety of additional problems during preschool age^[1]. As such, breathing abnormalities have often been described. They can have their onset already during the regression period and are characterised by episodes of breath holding, hyperventilation and air swallowing^[28,32]. Epileptic seizures are also common. Huppke and colleagues revealed that 40% of their study participants had developed epilepsy by the age of 5 years^[33]. Though, the severity of the seizures decreases when the patients become older and hardly ever causes problems after the age of 40 years^[25].

Scoliosis often develops from early school age and was found in 74% of the girls in the Swedish study^[28]. Other deformities are mainly present in the lower limbs, especially in the feet, which become "fixed in a rigid supinated flexed position"^[3, p.63]. Over the years muscle strength decreases and the muscles often become atrophic. The joint deformities and muscular insufficiency lead to deterioration of walking abilities and many patients are wheelchair bound in adulthood. Those who preserve ambulation have been found to have a longer survival time^[3,8,25].

Many girls also develop gastrointestinal problems. Swallowing dysfunction, gastrooesophageal reflux and constipation have often been described^[1,3]. A striking feature displayed by the patients is their seemingly decreased response to pain^[26,28,32]. Hagberg has found that reaction to pain is prolonged and can be abnormal^[3]. Though autistic features tend to diminish, many girls still show unusual behaviour. Parents often describe episodes of inappropriate screaming, crying and peculiar night laughter^[3,26,32].

The different symptoms of RTT will be further described in the following chapter.

References for 1.2.2 Clinical stages of classic RTT

- [1] Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.1-26.
- [2] Hagberg B, Witt Engerström I. The Swedish series of females with Rett syndrome 1960-92. In: Hagberg B, editor. *Rett syndrome - clinical and biological aspects*. London: Mac Keith Press; 1993. p.21-26.
- [3] Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002;8:61-65.
- [4] Nomura Y, Segawa M. Natural history of Rett syndrome. *J Child Neurol* 2005;20:764-68.
- [5] Naidu S. Rett syndrome: a disorder affecting early brain growth. *Ann Neurol* 1997;42(1):3-10.
- [6] Trevathan E, chairperson. Diagnostic criteria for Rett syndrome. The Rett Syndrome Diagnostic Criteria Work Group. *Ann Neurol* 1988;23(4):425-8.
- [7] Leonard H, Moore H, Carey M, Fyfe S, Hall S, Robertson L, et al. Genotype and early development in Rett

- syndrome: The value of international data. *Brain Dev* 2005;27 Suppl 1:59-68
- [8] Huppke P, Held M, Laccone F, Hanefeld F. The spectrum of phenotypes in females with Rett syndrome. *Brain Dev* 2003;25:346-51.
 - [9] Picker J, Yang R, Ricceri L, Berger-Sweeney J. An altered neonatal behavioural phenotype in *Mecp2* mutant mice. *Neuroreport* 2006;17(5):541-4.
 - [10] Nomura Y. Early behaviour characteristics and sleep disturbance in Rett syndrome. *Brain Dev* 2005;27 Suppl 1:35-42
 - [11] Segawa M. Early motor disturbances in Rett syndrome and its pathophysiological importance. *Brain Dev* 2005;27 Suppl 1:54-58.
 - [12] Santos M, Silva-Fernandes A, Oliveira P, Sousa N, Maciel P. Evidence for abnormal early development in a mouse model of Rett syndrome. *Genes Brain Behav* 2007;6(3):277-86.
 - [13] Fehr S, Bebbington A, Ellaway C, Rowe P, Leonard H, Downs J. Altered attainment of developmental milestones influences the age of diagnosis of rett syndrome. *J Child Neurol* 2011;26(8):980-7.
 - [14] Marschik PB, Einspieler C. Methodological note: video analysis of the early development of Rett syndrome-one method for many disciplines. *Dev Neurorehabil* 2011;14(6):355-7.
 - [15] Einspieler C, Kerr AM, Prechtl HF. Abnormal general movements in girls with Rett disorder: the first four months of life. *Brain Dev* 2005;27 Suppl 1:8-13.
 - [16] Piek J. Infant motor development. Champaign,IL: Human Kinetics; 2006. p.182-3.
 - [17] Temudo T, Maciel P, Sequeiros J. Abnormal movements in Rett syndrome are present before the regression period: a case study. *Mov Disord* 2007;22(15):2284-7.
 - [18] Einspieler C, Kerr AM, Prechtl HF. Is the early development of girls with Rett disorder really normal?. *Pediatr Res* 2005;57(5):696-700.
 - [19] Burford B, Kerr AM, Macleod HA. Nurse recognition of early deviation in development in home videos of infants with Rett disorder. *J Intellect Disabil Res* 2003;47(8):588-96.
 - [20] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;68(6):944-50.
 - [21] Marschik PB, Pini G, Bartl-Pokorny KD, Duckworth M, Gugatschka M, Vollmann R, et al. Early speech-language development in females with Rett syndrome: focusing on the preserved speech variant. *Dev Med Child Neurol* 2012;54(5):451-456.
 - [22] Marschik PB, Einspieler C, Sigafos J. Contributing to the early detection of Rett syndrome: the potential role of auditory Gestalt perception. *Res Dev Disabil* 2012;33(2):461-6.
 - [23] Marschik PB, Einspieler C, Oberle A, Laccone F, Prechtl HF. Case report: Retracing atypical development: a preserved speech variant of Rett syndrome. *J Autism Dev Disord* 2009;39(6):958-61.
 - [24] Burford B. Perturbations in the development of infants with Rett disorder and the implications for early diagnosis. *Brain Dev* 2005;27 Suppl 1:3-7.
 - [25] Hagberg B.J. Rett syndrome: long-term clinical follow-up experiences over four decades. *Child Neurol* 2005;20(9):722-7.
 - [26] Deidrick KM, Percy AK, Schanen NC, Mamounas L, Maria BL. Rett syndrome: pathogenesis, diagnosis, strategies, therapies, and future research directions. *J Child Neurol* 2005;20(9):708-17.
 - [27] Fiumara A, Barone R, D'Asero G, Marzullo E, Pavone L. Rett syndrome: photographic evidence of rapid regression. *J Child Neurol* 1999;14(8):550-2.
 - [28] Larsson G, Lindström B, Engerström IW. Rett syndrome from a family perspective: The Swedish Rett Center survey. *Brain Dev* 2005;27 Suppl 1:14-19.
 - [29] Knott M, Leonard H, Downs J. The diagnostic odyssey to Rett syndrome: The experience of an Australian family. *Am J Med Genet A* 2012;158A:10-12.
 - [30] Fehr S, Downs J, Bebbington A, Leonard H. Atypical presentations and specific genotypes are associated with a delay in diagnosis in females with Rett syndrome. *Am J Med Genet A* 2010;152A(10):2535-42.
 - [31] Temudo T, Oliveira P, Santos M, Dias K, Vieira J, Moreira A, et al. Stereotypes in Rett syndrome: analysis of 83 patients with and without detected MECP2 mutations. *Neurology* 2007;68(15):1183-7.
 - [32] Percy AK, Lane JB. Rett syndrome: model of neurodevelopmental disorders. *J Child Neurol* 2005;20(9):718-21.
 - [33] Huppke P, Held M, Hanefeld F, Engel W, Laccone F. Influence of mutation type and location on phenotype in 123 patients with Rett syndrome. *Neuropediatrics* 2002;33(2):63-8.
 - [34] Kerr AM, Prescott RJ. Predictive value of the early clinical signs in Rett disorder. *Brain Dev* 2005;27 Suppl 1:20-24.
 - [35] Lim F, Downs J, Li J, Bao XH, Leonard H. Barriers to diagnosis of a rare neurological disorder in China-Lived experiences of Rett syndrome families. *Am J Med Genet A* 2012;158A:1-9.
 - [36] Nomura Y, Segawa M. Clinical features of the early stage of the Rett syndrome. *Brain Dev.* 1990;12(1):16-9.

1.2.3 Symptoms

1.2.3.1 Breathing abnormalities

Abnormal breathing patterns have been commonly reported in individuals with RTT ever

since the discovery of the disease and are said to be the most distressing feature for both caregivers and patients. They mostly arise during regression but become prominent in the post-regression period and are then present throughout life^[1,2]. Initially the respiratory irregularities have been thought to occur exclusively during wakefulness^[2-5], yet recent studies have shown that awake-like breathing abnormalities are also present during sleep, although less frequently^[6].

The most common types of irregular breathing patterns described by parents are hyperventilation and breath-holding^[2,5,7,8]. In the British survey 78% of 408 patients were reported to show episodes of hyperventilation and 73% performed repetitive breath-holds^[2]. Aerophagia with subsequent abdominal distension, non-epileptic vacant spells and Valsalva manoeuvres have also often been described^[1,2,7]. During one-hour plethysmographic monitoring of breathing movements of 56 females with RTT, Julu and colleagues^[9] identified 13 different abnormal breathing patterns with each patient performing an average of 8 different abnormal rhythms. Contrary to earlier and less extensive studies which reported breathing disturbances in 76% to 93% of the patients^[2,8,10,11], the researchers observed abnormal respiratory behaviours in all study participants, even in those who were reported by the parents to have no breathing abnormalities^[9]. This indicates that abnormal breathing patterns might possibly be overlooked without accurate measurement.

The most recurrent breathing behaviours in the study of Julu and colleagues^[9] were outlined in three groups of cardiorespiratory phenotype namely apneustic (Figure 1.3), feeble/inadequate (Figure 1.4) and forceful breathing (Figure 1.5). Patients with apneustic breathing showed either breath holds - which sometimes occurred successively - or prolonged inspiration followed by abrupt expiration. These patterns were mostly seen in the youngest (under 5 years old) patients. Feeble breathing was characterised by shallow inspirations and expirations with a decrease of the depth of respiration or by central apnoea, which is a "cessation of breathing movements at the end of expiration"^[9, p.31]. Both above mentioned cardiorespiratory phenotypes lead to an inadequate ventilation and to retention of carbon dioxide in the body, the latter causing respiratory alkalosis. In contrast, patients with forceful breathing, marked by abnormally rapid or abnormally deep respiration^[9], exhale carbon dioxide excessively and are thus rather affected by respiratory acidosis^[1].

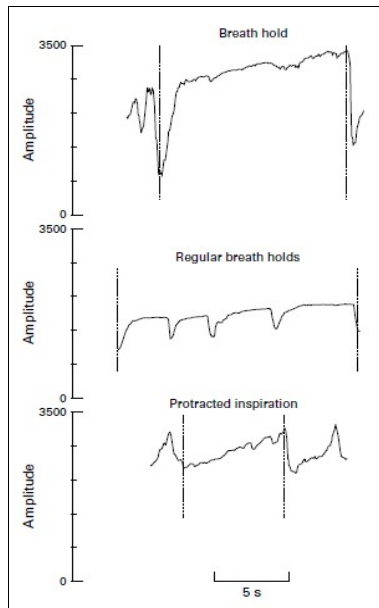


Figure 1.3: Apneustic breathing style[9].

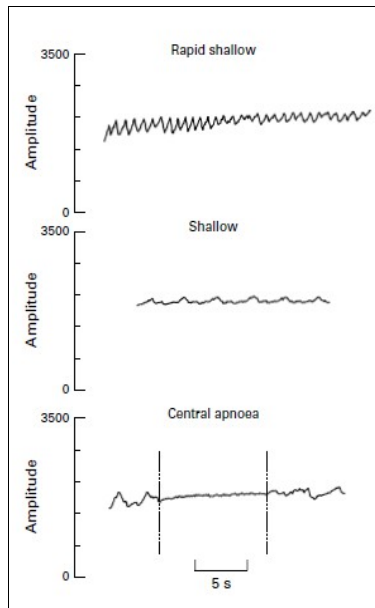


Figure 1.4: Feeble/inadequate breathing style[9].

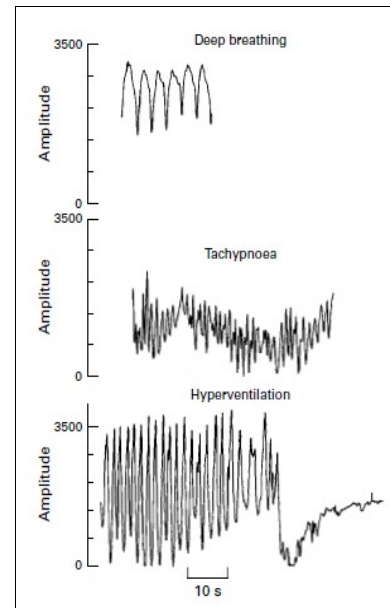


Figure 1.5: Forceful breathing style[9].

Though hyperventilation has commonly been described to occur more frequently when patients are agitated or stressed^[12-15], the occurrence of the other abnormal breathing rhythms has not been found to be associated with specific circumstances. Instead, patients tend to change in between their breathing behaviours at a random manner.

The exact pathomechanism of the respiratory dysfunction in RTT has not yet been understood. However, a variety of neurochemical factors which are important for the integration of the respiratory network have been found to be altered in RTT (see chapter 1.3.2 CNS malfunction in RTT) and these alterations may play a role in the development of breathing abnormalities^[16].

References for 1.2.3.1 Breathing abnormalities

- [1] Smeets EE, Pelc K, Dan B. Rett Syndrome. *Mol Syndromol* 2012;2(3-5):113-27.
- [2] Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.1-26.
- [3] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;68(6):944-50.
- [4] Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002;8(2):61-5.
- [5] Glaze DG. Neurophysiology of Rett syndrome. *J Child Neurol*. 2005 Sep;20(9):740-6.
- [6] Weese-Mayer DE, Lieske SP, Boothby CM, Kenny AS, Bennett HL, Ramirez JM. Autonomic dysregulation in young girls with Rett Syndrome during nighttime in-home recordings. *Pediatr Pulmonol* 2008;43(11):1045-60.
- [7] Larsson G, Lindström B, Engerström IW. Rett syndrome from a family perspective: The Swedish Rett Center survey. *Brain Dev* 2005;27 Suppl 1:14-19.
- [8] Amir RE, Van den Veyver IB, Schultz R, Malicki DM, Tran CQ, Dahle EJ, et al. Influence of mutation type and X chromosome inactivation on Rett syndrome phenotypes. *Ann Neurol* 2000;47(5):670-9.
- [9] Julu PO, Kerr AM, Apartopoulos F, Al-Rawas S, Engerström IW, Engerström L, et al. Characterisation of breathing and associated central autonomic dysfunction in the Rett disorder. *Arch Dis Child* 2001;85(1):29-37.
- [10] Didden R, Korzilius H, Smeets E, Green VA, Lang R, Lancioni GE, et al. Communication in individuals with Rett syndrome: an assessment of forms and functions. *J Dev Phys Disabil* 2010;22(2):105-18.
- [11] Halbach NS, Smeets EE, van den Braak N, van Roozendaal KE, Blok RM, Schrander-Stumpel CT, et al.

- Genotype-phenotype relationships as prognosticators in Rett syndrome should be handled with care in clinical practice. *Am J Med Genet A* 2012;158A(2):340-50.
- [12] Marschik PB, Einspieler C, Oberle A, Laccone F, Prechtl HF. Case report: Retracing atypical development: a preserved speech variant of Rett syndrome. *J Autism Dev Disord* 2009;39(6):958-61.
 - [13] Philippart M. Handwriting in Rett syndrome: a normal developmental stage. *Ped Neurol* 1992;8:197-9.
 - [14] Elian M, de M Rudolf N. Observations on hand movements in Rett syndrome: a pilot study. *Acta Neurol Scand* 1996;94(3):212-4.
 - [15] Lindberg B. *Understanding Rett syndrome: a practical guide for parents, teachers, and therapists*. Cambridge, MA: Hogrefe & Huber Publishers; 2006. p.35-37.
 - [16] Ogier M, Katz DM. Breathing dysfunction in Rett syndrome: understanding epigenetic regulation of the respiratory network. *Respir Physiol Neurobiol* 2008;164(1-2):55-63.

1.2.3.2 Difficulties in communication

Partial or complete loss of acquired speech is one of the main criteria for the diagnosis of RTT^[1]. It affects the vast majority of the patients as only about 10% maintain the ability to use some expressive language, ranging from babbling to speaking more than 10 words^[2,3]. An exception are patients with the Preserved Speech Variant who are more likely to retain their speech abilities or regain them after the regression period. They often display a broader vocabulary with more than 40 active words and are mostly able to produce phrases^[4,17,18].

Lindberg^[5] supposed that the absence of speech is caused by verbal apraxia. She experienced that sometimes the girls apparently wanted to say something but despite extreme concentration and repetitive mouth movements the words could not be uttered. She also revealed that the patients were more likely to vocalise and express word-like sounds when they were tired or asleep^[5]. Due to the topographic proximity of the motor speech areas and the area of hand representation in the neocortex, Belichenko suggested that language production might be affected by the same pathological mechanism as hand function^[6].

Parents and experts agree that the patients regain a great desire for social interaction and communication once "coming out" of the devastating period of regression^[5,7,8]. Different to patients with autism they prefer people to objects and love to be in company, especially with other children who they like to watch and listen to their singing. Yet, due to their inability to speak or use their hands for gestures they are severely handicapped in expressing themselves and are thus often misunderstood^[5]. However, especially parents learn to comprehend their child's alternative ways of communication. In a study of 39 females with RTT, Lindberg^[5] revealed that almost all patients could demonstrate that they wanted to eat when they were sitting at the table with the food in view. About one third could display their wish for food by more advanced means such as walking to the fridge or

staring at the stove. One half of the 39 participants was able to communicate other desires. One girl would close her mouth during feeding and stare at the glass when she wanted to drink instead. Another patient would tap her coat to show that she wanted to go for a walk. Most patients were able to demonstrate rejection by avoiding eye contact, displaying postural stiffness, crying or falling asleep^[5]. Using parental questionnaires, Larsson and colleagues revealed that 65% of 115 study participants could express their will, although the ways of communication were not reported^[9]. While Lavas and colleagues^[10] revealed that more than one third of their 125 study participants used symbolic communication forms such as words, pictures or gestures to express themselves, Didden and colleagues reported that symbolic communication was rarely performed by the 120 patients in their study. They found that the most common ways of expression were pre-linguistic and non-symbolic with eye-pointing being the most frequently used^[11]. The latter was consistent with the findings of many other researchers^[5,10,12-15]. Cass and colleagues revealed that about two thirds of their 87 study participants used their eyes as a mean of communication^[12]. In a study of 125 children and adults with RTT, Lavas and colleagues found that 90% could express their needs by eye-pointing^[10]. This way of communication has even been found in severely affected patients and seems to substitute their lack of other communication skills^[5,13,14].

The extent of comprehension of words and language among patients with RTT is difficult to be assessed as most patients are unable to respond by speech or action. Yet, many parents are convinced that the girls understand more than they are thought to be capable of^[13,16]. There have been reports about patients who showed accurate emotions in different situations, although it remained unclear whether they understood the conversation itself or they reacted to facial expressions and emotions of adults^[13,16]. However, Lindberg^[16] revealed that many of the 39 females in her study showed adequate emotions even though she talked to them in an emotionally neutral tone. Furthermore, some parents of her study participants reported that their children were less anxious in new circumstances or when getting in contact with strangers if they were told about the situation in advance. A mother mentioned that her girl was afraid of cars but could handle her fear if she informed her before a car was passing by^[16].

Though many parents are able to understand certain demands of their child, the lack of usual communication is one of the most burdening features for them. Lindberg revealed that the most predominant wish of caretakers was to find possibilities to better interpret the

patients' feelings and needs^[5].

References for 1.2.3.2 Difficulties in communication

- [1] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;68(6):944-50.
- [2] Huppke P, Held M, Laccone F, Hanefeld F. The spectrum of phenotypes in females with Rett syndrome. *Brain Dev* 2003;25:346-51.
- [3] Huppke P, Held M, Hanefeld F, Engel W, Laccone F. Influence of mutation type and location on phenotype in 123 patients with Rett syndrome. *Neuropediatrics* 2002;33(2):63-8.
- [4] Zappella M, Gillberg C, Ehlers S. The preserved speech variant: a subgroup of the Rett complex: a clinical report of 30 cases. *J Autism Dev Disord* 1998;28(6):519-26.
- [5] Lindberg B. Understanding Rett syndrome: a practical guide for parents, teachers, and therapists. Cambridge,MA: Hogrede & Huber Publishers; 2006. p.60-70.
- [6] Belichenko PV. The morphological substrate for communication. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.277-301.
- [7] Deidrick KM, Percy AK, Schanen NC, Mamounas L, Maria BL. Rett syndrome: pathogenesis, diagnosis, strategies, therapies, and future research directions. *J Child Neurol* 2005;20(9):708-17.
- [8] Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.1-26.
- [9] Larsson G, Lindström B, Engerström IW. Rett syndrome from a family perspective: The Swedish Rett Center survey. *Brain Dev* 2005;27 Suppl 1:14-19.
- [10] Lavås J, Slotte A, Jochym-Nygren M, van Doorn J, Engerström IW. Communication and eating proficiency in 125 females with Rett syndrome: The Swedish Rett Center Survey. *Disabil Rehabil* 2006;28(20):1267-79.
- [11] Didden R, Korzilius H, Smeets E, Green VA, Lang R, Lancioni GE, et al. Communication in individuals with Rett syndrome: an assessment of forms and functions. *J Dev Phys Disabil* 2010;22(2):105-18.
- [12] Cass H, Reilly S, Owen L, Wisbeach A, Weekes L, Slonims V, et al. Findings from a multidisciplinary clinical case series of females with Rett syndrome. *Dev Med Child Neurol* 2003;45(5):325-37.
- [13] Smeets EE, Pelc K, Dan B. Rett Syndrome. *Mol Syndromol* 2012;2(3-5):113-27.
- [14] Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002;8:61-5.
- [15] Hetzroni OE, Rubin C. Identifying patterns of communicative behaviours in girls with Rett syndrome. *Augment Altern Commun* 2006;22(1):48-61.
- [16] Lindberg B. Understanding Rett syndrome: a practical guide for parents, teachers, and therapists. Cambridge,MA: Hogrede & Huber Publishers; 2006. p. 50-59.
- [17] Marschik PB, Einspieler C, Prechtel HF, Oberle A, Laccone F. Relabelling the preserved speech variant of Rett syndrome?. *Dev Med Child Neurol* 2010;52(2):218.
- [18] Marschik PB, Einspieler C, Oberle A, Laccone F, Prechtel HF. Case report: Retracing atypical development: a preserved speech variant of Rett syndrome. *J Autism Dev Disord* 2009;39(6):958-61.

1.2.3.3 Deviations in gross motor performance

Abnormalities and problems in the execution of gross motor skills are common among patients with RTT^[1-5]. In a considerable number of cases, they can already be observed during infancy as the girls are often delayed in the achievement of important milestones such as sitting, standing or walking or do not gain these abilities at all^[4,6,7]. In the regression period, some of the skills are lost completely or can only be performed with difficulties^[4,5]. About half of the patients maintain or retrain the ability to walk and some even learn this skill after the regression period^[4,5,8]. However, a variety of gait abnormalities can be observed in the majority of the girls. Generally, the gait is ataxic and, especially among older patients, often rigid. Most of the girls have difficulties in balancing their body weight due to truncal ataxia, abnormal muscle tone, perceptual problems and scoliosis^[3,9,10]. Thus, many prefer to walk on tip toe (digitigrade gait) and with extended lower limbs,

giving them greater stability. Others have their legs extended as well, but keep their heel in contact with the ground throughout the stance phase (plantigrade gait) and move forwards by side-to-side body rocking. A broad based gait is commonly seen, especially in girls with a plantigrade gait. Patients with digitigrade gait often use one leg as foremost leg which might make them go in circles^[10]. Standing seems to be difficult for most patients with RTT and those who normally walk on tip toe often depend on support while standing while those who normally have a plantigrade gait remain body rocking even while standing in order to keep their balance^[8-10]. Equilibrium response is often poor and Lindberg found an absence of backward protective reaction in all and undeveloped lateral and forward responses in many of her 39 study participants^[9].

Independent sitting is mostly retained in younger women but can get difficult as the diseases progresses due to low muscle strength and advanced scoliosis^[5,9].

Though a considerable percentage of patients with RTT can walk and sit unaided^[4,5,8], only a minority is able to execute more complex tasks such as transition movements. In a video study of 99 females with RTT, Downs and colleagues revealed that "the majority of children required assistance and some required lifting when getting in and out of a chair at mealtime and getting up from the floor to a chair or to an upright position"^[8, p.209]. Only 13.5% of their study participants were able to bend forwards and touch the floor unaided, whereas 84.6% needed maximum assistance to perform this task^[8]. In a study by Larsson and colleagues, less than half of 122 families reported that their daughter could sit down from standing or rise from sitting. Furthermore, patients had more difficulties in lying down from sitting than in moving to sitting from a lying position^[4].

As the patients grow older, postural deformities such as scoliosis or pes equinus and increased rigidity lead to a decrease of gross motor abilities^[1,9,11,12]. In a video study analysing the gross motor skills of 70 girls and women with RTT over a 3- to 4-year period, Foley and colleagues found that the highest scores of loss of gross motor skills were among the 8- to 14-year-old patients, while women older than 19 years were more likely to retain their abilities. Yet, the researchers admit that these results might be biased due to the already lower skill levels in older patients^[2].

Analysing the correlations between changes in gross motor skills and specific *MECP2* mutation types, Foley and colleagues revealed that patients with a p.R294X, C-terminal or p.R133C mutation showed the largest decrease in gross motor performance, although these mutations have earlier been associated with milder phenotypes. The researchers ascribed

this contradictory findings to better skill levels of these patients at the time of the first observation^[2].

Though about one fifth of 30 patients in a study by Witt-Engerström and Hagberg maintained ambulant into middle age^[13], the progress of a variety of comorbidities and postural abnormalities usually leads to complete wheelchair bondage when the patients get older^[1,3,9]. Yet, some cases of women who learned to walk at advanced age or even after some time of wheelchair use have been described^[14,15]. Physical therapy is essential in order to maintain and improve ambulation in RTT, as ambulant patients have been found to have a better survival rate and a lower risk for developing scoliosis^[11]. However, physical therapy in RTT is often difficult as the majority of the patients have problems in coping with external facilitation and therapists need to have a good knowledge about the disease in order to properly address the girls' special needs^[1,16].

References for 1.2.3.3 Deviations in gross motor performance

- [1] Lotan M, Hanks S. Physical therapy intervention for individuals with Rett syndrome. *Scientific World Journal* 2006;6:1314-38.
- [2] Foley KR, Downs J, Bebbington A, Jacoby P, Girdler S, Kaufmann WE, et al. Change in gross motor abilities of girls and women with rett syndrome over a 3- to 4-year period. *J Child Neurol.* 2011 Oct;26(10):1237-45.
- [3] Temudo T. Movement disorders in Rett syndrome. In: Nardocci N, Fernandez-Alvarez E, editors. *Movement disorders in children: a clinical update with video recordings.* Montrouge. Editions John Libbey Eurotext; 2007. p.153-167.
- [4] Larsson G, Lindström B, Engerström IW. Rett syndrome from a family perspective: The Swedish Rett Center survey. *Brain Dev* 2005;27 Suppl 1:14-19.
- [5] Huppke P, Held M, Hanefeld F, Engel W, Laccone F. Influence of mutation type and location on phenotype in 123 patients with Rett syndrome. *Neuropediatrics* 2002;33(2):63-8.
- [6] Segawa M. Early motor disturbances in Rett syndrome and its pathophysiological importance. *Brain Dev* 2005;27(1):54-58.
- [7] Leonard H, Moore H, Carey M, Fyfe S, Hall S, Robertson L, et al. Genotype and early development in Rett syndrome: The value of international data. *Brain Dev* 2005;27:59-68
- [8] Downs JA, Bebbington A, Jacoby P, Msall ME, McIlroy O, Fyfe S, et al. Gross motor profile in rett syndrome as determined y video analysis. *Neuropediatrics* 2008;39(4):205-10.
- [9] Lindberg B. *Understanding Rett syndrome: a practical guide for parents, teachers, and therapists.* Cambridge,MA: Hogrede & Huber Publishers; 2006. p.37-44.
- [10] Dan B, Cheron B: Postural control in children with Rett syndrome or Angelman syndrome. In Hadders-Algra M, Brogren Carlberg E, editors. *Posture: A Key Issue in Developmental Disorders.* Cambridge: Mac Keith Press; 2008. p.148–169.
- [11] Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002;8:61-65.
- [12] Smeets EE, Pelc K, Dan B. Rett Syndrome. *Mol Syndromol* 2012;2(3-5):113-127.
- [13] Witt-Engerström I. Hagberg, B. The Rett syndrome: gross motor disability and neural impairments in adults. *Brain Dev* 1990;12:33-36.
- [14] Larsson G, Engerström IW. Gross motor ability in Rett syndrome-the power of expectation, motivation and planning. *Brain Dev* 2001;23 Suppl 1:77-81.
- [15] Jacobsen K, Viken A, von Tetzchner S. Rett syndrome and ageing: a case study. *Disabil Rehabil* 2001;23(3-4):160-6.
- [16] Mount RH, Hastings RP, Reilly S, Cass H, Charman T. Behavioural and emotional features in Rett syndrome. *Disabil. Rehabil* 2001;23:129–138.

1.2.3.4 Spinal deformities

Spinal deformities such as scoliosis or kyphosis affect between 50% and 90% of all

patients with RTT and are included in the list of supportive criteria for diagnosis^[1,2]. Scoliosis usually starts to develop in mid-childhood when the girls enter the post-regression period and partly seems to be caused by postural asymmetry and abnormal overall muscle tone as it occurs most often in patients with dystonia, hypertonia or hypotonia^[3-5]. Several researchers also found a correlation between the development of scoliosis and the patients' ambulation skills: Individuals who never achieved ambulation or lost it during regression are much more likely to develop scoliosis than those with preserved walking ability^[1,3,6,7]. At the same time the spinal deformity itself can lead to a loss of ambulation skills. Riise^[8] and colleagues revealed that especially patients with a C-shaped curve are severely restricted in ambulation. Of their 29 mutation positive study participants, 15 displayed a C-shaped curve and only two out of the 15 could walk with support. In contrast, seven of the nine patients with a double-shaped curve had some preserved ambulation skills and all four patients without scoliosis could walk independently^[8]. Ambulant patients in turn are more likely to develop kyphosis which, according to Smeets, is caused by their repetitive bending forward on extended legs in order to maintain their balance^[3,8].

Although Riise and colleagues only described a weak correlation between age and curve size^[8], the majority of researchers found that the scoliosis usually progresses constantly even after skeletal maturation^[4-7,9,10]. In a study of 554 patients with RTT, Percy and colleagues revealed that the mean age for individuals with scoliosis was 15 years while the mean age for those without scoliosis was 6 years^[7]. Halbach and colleagues reported that among the 137 mutation-positive females in their study the majority of the those younger than 10 years had no scoliosis in contrast to only 10% of the patients older than 10 years^[9]. Temudo and colleagues found that the prevalence of scoliosis was much higher in the group of patients who developed the RTT phenotype at least 60 months earlier compared to those with a shorter duration of the disease^[5].

Correlation studies between the presence of scoliosis and certain mutation types have led to contradictory results. While Halbach and colleagues identified no significant differences in the prevalence of scoliosis for the most common mutation types^[9], Amir and colleagues revealed higher occurrence rates in patients with missense mutations^[11]. In contrast, Temudo and colleagues reported that all patients with truncating mutations and a duration of the disease of at least 60 months had developed scoliosis compared to only 82.4% of those with missense mutations^[5].

The therapeutic options for spinal deformities in RTT are limited. As loss of ambulation has been found to be associated with a higher risk for the development of scoliosis, exercises which might improve or maintain the patients' abilities to walk are indicated. Physiotherapy can be an option yet has been found to have little effect on the progress of spinal deformities. Additional use of spinal braces may lead to a deceleration of the progression but very often a complicated spinal fusion surgery is inevitable, especially when pulmonary function is restricted by the scoliosis or the deformity causes heavy pains^[1,4].

Until recently, the evidence based information on the management of scoliosis in patients with RTT was limited to a small number of case series^[12-15]. In order to create the first guidelines for early detection, monitoring and therapy Downs and colleagues asked a group of 60 experts on the field of RTT if they "strongly agree, agree, neither agree or disagree, disagree [or] strongly disagree"^[16, p.E608] with different statements withdrawn from the existing literature and from emails exchanged among parents via Rettnet, a RTT-specific email list serve^[17]. The experts' consensus together with the findings from literature were then published in 2009 as 'Guidelines for management of scoliosis in Rett Syndrome patients based on expert consensus and clinical evidence'^[16].

References for 1.2.3.4 Spinal deformities

- [1] Koop SE. Scoliosis and Rett syndrome. *Dev Med Child Neurol* 2011;53(7):582-3.
- [2] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;68(6):944-50.
- [3] Smeets EE, Pelc K, Dan B. Rett Syndrome. *Mol Syndromol* 2012;2(3-5):113-27.
- [4] Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.1-26.
- [5] Temudo T, Ramos E, Dias K, Barbot C, Vieira JP, Moreira A, et al. Movement disorders in Rett syndrome: an analysis of 60 patients with detected MECP2 mutation and correlation with mutation type. *Mov Disord* 2008;23(10):1384-90.
- [6] Temudo T. Movement disorders in Rett syndrome. In: Nardocci N, Fernandez-Alvarez E, eds. *Movement disorders in children: a clinical update with video recordings*. Montrouge: John Libbey Eurotext; 2007. p.153-165.
- [7] Percy AK, Lee HS, Neul JL, Lane JB, Skinner SA, Geerts SP, et al. Profiling scoliosis in Rett syndrome. *Pediatr Res* 2010;67(4):435-9.
- [8] Riise R, Brox JI, Sorensen R, Skjeldal OH. Spinal deformity and disability in patients with Rett syndrome. *Dev Med Child Neurol* 2011;53(7):653-7.
- [9] Halbach NS, Smeets EE, van den Braak N, van Roozendaal KE, Blok RM, Schrander-Stumpel CT, et al. Genotype-phenotype relationships as prognosticators in Rett syndrome should be handled with care in clinical practice. *Am J Med Genet A* 2012;158A(2):340-50.
- [10] Hoffbuhr K, Devaney JM, LaFleur B, Sirianni N, Scacheri C, Giron J, et al. MeCP2 mutations in children with and without the phenotype of Rett syndrome. *Neurology* 2001;56(11):1486-95.
- [11] Amir RE, Van den Veyver IB, Schultz R, Malicki DM, Tran CQ, Dahle EJ, et al. Influence of mutation type and X chromosome inactivation on Rett syndrome phenotypes. *Ann Neurol* 2000;47(5):670-9.
- [12] Bassett GS, Tolo VT. The incidence and natural history of scoliosis in Rett syndrome. *Dev Med Child Neurol* 1990;32(11):963-6.
- [13] Harrison DJ, Webb PJ. Scoliosis in the Rett syndrome: natural history and treatment. *Brain Dev* 1990;12(1):154-6.
- [14] Hanks SB. Motor disabilities in the Rett syndrome and physical therapy strategies. *Brain Dev* 1990;12(1):157-61.
- [15] Kerr AM, Webb P, Prescott RJ, Milne Y. Results of surgery for scoliosis in Rett syndrome. *J Child Neurol*

- 2003;18(10):703-8.
- [16] Downs J, Bergman A, Carter P, Anderson A, Palmer GM, Roye D, et al. Guidelines for management of scoliosis in Rett syndrome patients based on expert consensus and clinical evidence. *Spine* 2009;34(17):E607-17.
 - [17] International Rett Syndrome Foundation. Online Communities - RettNet. <http://www.rett syndrome.org/content/view/218/495>; accessed November 30th, 2012.
 - [18] Hagberg B.J. Rett syndrome: long-term clinical follow-up experiences over four decades. *Child Neurol* 2005;20(9):722-7.

1.2.3.5 Epilepsy

Epilepsy is one of the main comorbidities in RTT, affecting between 70% and 90% of all patients with classic and variant forms^[1-6]. Seizures normally start at a median age of 48 months, when patients have entered stage III of the disease^[1]. Yet, girls with the Early Seizure Variant of RTT - associated with mutations in the *CDKL5* gene - display epileptic seizures much earlier, often already before the 5th month of life^[7]. Also, male descendants from family cases of RTT are commonly affected by severe neonatal encephalopathy and develop epilepsy already during infancy^[8,9]. The age of seizure onset has been shown to serve as a prognostic factor for the course of the epilepsy. Nissenkorn and colleagues revealed that epilepsy was intractable in 64% of the 42 patients with seizure onset before the age of 5 years, whereas it was well controlled in 60% of the 20 individuals with later seizure onset. Furthermore, patients with early seizure onset showed a higher incidence of febrile seizures preceding epilepsy, status epilepticus and ESES (Electrical Status Epilepticus in Sleep)^[3,6]. Regardless of the age of onset, the frequency of seizures per month seems to be age dependent. The highest incidence of seizures per month has been found in girls between 7 and 12 years of age. Later, seizures tend to occur less frequently and women over 20 years have shown monthly seizure rates almost equal to those found in patients younger than 7 years^[2]. Furthermore, after the age of 20 years, the seizures are prone to be rather partial than generalised and patients are rarely affected by more than one seizure type^[3]. In contrast, younger patients show a broad spectrum of different seizure types such as partial, generalised or secondarily generalised and a single patient may be affected by two or more different types. In a Swedish study of 53 patients, 14% displayed three or more different seizure types^[3].

The onset of epilepsy is usually preceded by the appearance of abnormal EEG patterns during the regression period. These abnormal patterns include a general slowing with an excess of gamma and theta waves and the occurrence of epileptiform discharges. Yet, an abnormal EEG is no predictor for the development of epilepsy as epileptogenic activity has been found in EEGs of both patients with and without seizures^[10]. Still, EEG recordings are

important to distinguish between epileptic seizures and nonepileptic paroxysmal events such as vacant spells, episodic laughing or crying or periodic hyperventilation which occur frequently in RTT and are often reported as seizures by the parents^[4].

Several features of RTT have been associated with the risk of developing epilepsy as well as with the frequency of seizures per month^[1,2]. Patients with reported abnormal development within the first 10 months of life have been found to develop epilepsy twice as often and have average seizure rates twice as high as patients with apparently normal development. Patients who are able to walk unaided have demonstrated a twofold lower risk for the development of epilepsy and four times less seizure events per month than those who had never achieved ambulation^[1,2]. Increased rates of seizures have also been found in girls and women with low body mass index, high severity scores and poor functional ability^[1].

Correlation studies of *MECP2* mutation status and the incidence and age of onset of epilepsy have come to contradictory results. In their retrospective study of 602 patients, Glaze and colleagues revealed that 73% of their *MECP2* mutation negative patients had a history of epilepsy compared to only 53% of those with *MECP2* mutations^[4]. Jian and colleagues reported an earlier onset of seizures in patients with no detected *MECP2* mutations^[1]. However, excluding patients with the Early Seizure Variant, Nissenkorn and colleagues found no difference between *MECP2* mutation positive and *MECP2* mutation negative patients in their study^[6]. Some researchers have described correlations between specific *MECP2* mutations and the incidence and time of onset of epilepsy: p.R294X, p.R255X and C-terminal mutations have been associated with lower seizure rates^[2], p.R168X, p.R294X and C-terminal mutations with a lower incidence of seizures within the first 48 months of life^[1] and p.R255X and p.R306C mutations with a lower incidence of epilepsy overall^[4]. A higher incidence of epilepsy has been found in patients with a p.T158M mutation^[4]. Analysing 275 cases with epilepsy registered in the Australian Rett Database, Jian and colleagues revealed that patients with p.R255X mutations had the earliest and patients with p.R294X the latest onset of epilepsy at a median age of 37 months and, respectively, 76 months^[1].

Skewed X-inactivation has been found to have a positive effect on the onset and the frequency of epileptic seizures, as these patients showed lower seizure rates and a lower incidence of seizures within the first 48 months of life, although the researchers did not report which allele was predominantly active in their patients^[1,2].

Most RTT patients with epilepsy are treated with antiepileptic drugs (AED) and only few, severe cases require adjunctive treatment methods such as vagus nerve stimulation or ketogenic diet^[4]. Sodium valproate and carbamazepine as older anticonvulsants have shown good results both as monotherapy as well as in combination with each other^[2]. Among the new AEDs, lamotrigine is the most commonly used, though Jian and colleagues found higher rates of seizures in those treated with lamotrigine as monotherapy or in combination with other anticonvulsants compared to those treated with sodium valproate or carbamazepine^[2]. Monotherapy is insufficient for about half of the patients with epilepsy and RTT and about 10% require treatment with three or more AEDs. Kim and colleagues revealed that in many patients a treatment is effective, as 42.9% of their 20 study participants with epilepsy became seizure free due to permanent anticonvulsant medication^[5].

References for 1.2.3.5 Epilepsy

- [1] Jian L, Nagarajan L, de Klerk N, Ravine D, Bower C, Anderson A, et al. Predictors of seizure onset in Rett syndrome. *J Pediatr* 2006;149(4):542-7.
- [2] Jian L, Nagarajan L, de Klerk N, Ravine D, Christodoulou J, Leonard H. Seizures in Rett syndrome: an overview from a one-year calendar study. *Eur J Paediatr Neurol* 2007;11(5):310-7.
- [3] Steffenburg U, Hagberg G, Hagberg B. Epilepsy in a representative series of Rett syndrome. *Acta Paediatr* 2001;90(1):34-9.
- [4] Glaze DG, Percy AK, Skinner S, Motil KJ, Neul JL, Barrish JO, et al. Epilepsy and the natural history of Rett syndrome. *Neurology* 2010;74(11):909-12.
- [5] Kim HJ, Kim SH, Kim HD, Lee JS, Lee YM, Koo KY, et al. Genetic and epileptic features in Rett syndrome. *Yonsei Med J* 2012;53(3):495-500.
- [6] Nissenkorn A, Gak E, Vecsler M, Reznik H, Menascu S, Ben Zeev B. Epilepsy in Rett syndrome-the experience of a National Rett Center. *Epilepsia* 2010;51(7):1252-8.
- [7] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;68(6):944-50.
- [8] Schüle B, Armstrong DD, Vogel H, Oviedo A, Francke U. Severe congenital encephalopathy caused by MECP2 null mutations in males: central hypoxia and reduced neuronal dendritic structure. *Clin Genet* 2008;74(2):116-26.
- [9] Villard L. MECP2 mutations in males. *J Med Genet* 2007;44(7):417-23.
- [10] Cooper RA. The electroencephalogram in Rett syndrome. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.269-73.

1.2.3.6 Other symptoms

Autistic features and mood disturbances

Autism-like behaviours have commonly been described in individuals with RTT and, especially before the widespread recognition of RTT, patients were often misdiagnosed with autism^[1-7]. Although autistic features are most prominent during the regression period and ameliorate later in life, they are still present even in older individuals^[2,8]. Patients have been reported to get agitated or angry when daily routines are changed or become frightened when they are confronted with unfamiliar situations or noisy environments^[2,9]. They might then "shut down" all perceptual pathways and become completely

unresponsive to their surroundings^[9].

Patients with RTT have also been described to show sudden mood disturbances which are characterised by unprovoked anger, sadness or laughter or sudden changes of mood without any apparent reason^[1,2,10,11]. Some patients display episodes of sudden and violent screaming which can last for hours and are thought to be a signal of heavy body pains. Yet, thorough examinations have failed to identify any particular pathology that could explain these attacks^[11-13].

Deficits in integrating sensory information

Vision is probably one of the most intact senses in individuals with RTT^[9,14]. Besides the common occurrence of refractive errors, it has been described to be widely normal and patients are usually spared from optic nerve atrophy or cortical blindness which are often found in people with cognitive impairments^[14]. Still, Lindberg revealed that many patients seem to have difficulties to properly integrate visual impressions. They often stop when colours or ornaments of the floor or the type of flooring changes. Furthermore, they have difficulties in evaluating the height of an obstacle and even door thresholds can become an insurmountable hurdle to them^[9].

Patients are often reported to have a high pain threshold and delayed nociception^[1,11,12]. Yet, this behaviour can differ from day to day and also depends on the location of the stimulus. 'Internal' pain (such as stomach-ache or bowel complaint) seems to cause more discomfort than externally induced pain (such as injections). Furthermore, different body parts appear to have different levels of sensitivity. The face seems to be especially irritable in girls with RTT and parents have described that their daughters do not like to be touched in the face and show strong discomfort when the face is exposed to wind, snow or rain^[9].

Stereotypies

Although abnormal repetitive hand movements are the most common stereotypies in RTT (see chapter 1.4.2 The hands in RTT), some other peculiar stereotypic behaviours have been observed. Bruxism has been described by several researchers and was found in some 90% of 83 patients in a study by Temudo and colleagues^[11,12,15,16]. If excessively performed, this tooth grinding behaviour can cause dental attrition and might require botulinum toxin infiltration^[12]. Other stereotypies occur much less frequently and mainly involve the face, the head or the whole body. Patients have been reported to show repetitive eye closing, grimacing, head retropulsion or lip protrusion. A little more than 20% of the 83 participants

in a study by Temudo and colleagues showed repetitive trunk rocking or shifting of body weight from one leg to the other leg^[16]. Vocal stereotypies such as echolalia or repetitive sound production have been observed in some patients^[2,17].

Feeding difficulties

Feeding has been described to be difficult in many patients with RTT. In a study by Motil and colleagues, parents reported feeding problems in 81% of the 983 study participants^[18]. Placing the food into the mouth might be hindered by constant mouthing of the hands or stereotypic tongue movements^[1]. Lindberg reported that many patients have a very sensitive mouth and only tolerate smashed food with moderate temperature^[9]. The coordination of oral movements is often impaired and, especially in older patients, muscles tone is increased which hampers chewing and swallowing^[1]. More than half of the patients in the study by Motil and colleagues were found to have chewing problems and about 40% had difficulties with swallowing. Due to these impairments the feeding time is commonly prolonged and it might take patients one hour to finish a normal meal^[18].

Autonomic disturbances

There are several features in RTT that indicate a dysfunction of the autonomic nervous system. Peripheral blood circulation seems to be impaired as many patients have been described to have cold or even bluish feet^[5,11-13]. In a study by Larsson, 93% of 113 participants were reported to have cold feet and 66% of 78 participants had bluish/red feet^[5]. Halbach and colleagues revealed atrophic changes in the extremities in 22% of 137 females with RTT^[13]. Constipation, affecting about 80% of the patients, has been suggested as another indicator for autonomic dysfunction^[18-20].

Measuring cardiac vagal tone (CVT) with a Neuroscope in 45 girls with classic RTT, Julu and colleagues^[19] found that CVT was significantly lower in patients with RTT than in healthy controls both under normal circumstances as well as during abnormal breathing. Considering these results they suggested that the autonomic disturbances might partly be caused by a insufficient parasympathetic restraint^[19].

Glaze and Schultz^[21] revealed abnormal QT_c intervals in the electrocardiograms (ECG) of 59 patients. They found that QT_c values were longer in individuals with RTT when compared to healthy girls. Furthermore, several participants had abnormally prolonged QT_c intervals (>0.45 s) with a higher incidence in older patients. The researchers suggest that these abnormalities might contribute to the considerable high amount of sudden,

unexpected cases of death in RTT^[21].

Cognitive impairments

Due to their impaired communicative abilities it is difficult to assess cognitive function in individuals with RTT. Rett and Olson suggested that, concerning Piaget's theory of cognitive development^[23], patients would at best reach stage 4 on the sensorimotor intelligence scale^[22]. Yet one needs to consider that this scale is mostly based on motor performance which is severely impaired in RTT. Lindberg supposed that cognitive development would stagnate with the onset of regression and that patients would retain the achieved neurodevelopmental level throughout life^[24].

In a study of 39 girls and women, Lindberg^[24] described several participants who were apparently able to understand speech and pictures. She mentioned one experiment in which she placed different coloured photographs - always two at a time - in front of a participant and talked about the content of one of the pictures. The girl seemingly understood both the speech and the photographs as she always looked at the picture in question. Baptista and colleagues^[25] performed a similar experiment, yet using eyetracking technology and giving verbal instructions. They revealed that all except one of the seven girls in their study followed the instructions correctly and looked at the right picture. Yet, when asked to identify identical or similar pictures, only three participants could complete the task^[25].

Lindberg further observed that other cognitive abilities such as conception of space, time or causal relations were often more severely impaired than understanding of speech and pictures^[24].

References for 1.2.3.6 Other symptoms

- [1] Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. Rett disorder and the developing brain. Oxford: Oxford University Press; 2001. p.1-26.
- [2] Marschik PB, Einspieler C, Oberle A, Laccone F, Prechtl HF. Case report: Retracing atypical development: a preserved speech variant of Rett syndrome. J Autism Dev Disord 2009;39(6):958-61.
- [3] Hagberg B.J. Rett syndrome: long-term clinical follow-up experiences over four decades. Child Neurol 2005;20(9):722-7.
- [4] Fiumara A, Barone R, D'Asero G, Marzullo E, Pavone L. Rett syndrome: photographic evidence of rapid regression. J Child Neurol 1999;14(8):550-2.
- [5] Larsson G, Lindström B, Engerström IW. Rett syndrome from a family perspective: The Swedish Rett Center survey. Brain Dev 2005;27 Suppl 1:14-19.
- [6] Trevathan E, chairperson. Diagnostic criteria for Rett syndrome. The Rett Syndrome Diagnostic Criteria Work Group. Ann Neurol 1988;23(4):425-8.
- [7] Lim F, Downs J, Li J, Bao XH, Leonard H. Barriers to diagnosis of a rare neurological disorder in China-Lived experiences of Rett syndrome families. Am J Med Genet A 2012;158A:1-9.
- [8] Kaufmann WE, Tierney E, Rohde CA, Suarez-Pedraza MC, Clarke MA, Salorio CF, et al. Social impairments in Rett syndrome: characteristics and relationship with clinical severity. J Intellect Disabil Res 2012;56(3):233-47.
- [9] Lindberg B. Understanding Rett syndrome: a practical guide for parents, teachers, and therapists. Cambridge,MA: Hogrefe & Huber Publishers; 2006. p.22-31.
- [10] Mount R, Hastings R, Charman T, reilly S, Cass H. Behavioural and emotional features of Rett syndrome. In:

- Kerr A, Witt Engerström I, editors. Rett disorder and the developing brain. Oxford: Oxford University Press; 2001. p-339-342.
- [11] Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002;8:61-65.
 - [12] Smeets EE, Pelc K, Dan B. Rett Syndrome. *Mol Syndromol* 2012;2(3-5):113-127.
 - [13] Halbach NS, Smeets EE, van den Braak N, van Roozendaal KE, Blok RM, Schrandt-Stumpel CT, et al. Genotype-phenotype relationships as prognosticators in Rett syndrome should be handled with care in clinical practice. *Am J Med Genet A* 2012;158A(2):340-50.
 - [14] McCulloch D, Henderson R, Suanders K, Walley R. Vision in rett syndrome: studies using evoked potentials and event-related potentials. In: Kerr A, Witt Engerström I, editors. Rett disorder and the developing brain. Oxford: Oxford University Press; 2001. p.343-348.
 - [15] Temudo T. Movement disorders in Rett syndrome. In: Nardocci N, Fernandez-Alvarez E, editors. Movement disorders in children: a clinical update with video recordings. Montrouge. Editions John Libbey Eurotext; 2007. p.153-167.
 - [16] Temudo T, Oliveira P, Santos M, Dias K, Vieira J, Moreira A, et al. Stereotypies in Rett syndrome: analysis of 83 patients with and without detected MECP2 mutations. *Neurology* 2007;68(15):1183-7.
 - [17] Temudo T, Freitas P, Sequeiros J, Maciel P, Oliveira G. Atypical stereotypies and vocal tics in Rett syndrome: An illustrative case. *Mov Disord* 2008;23(4):622-4.
 - [18] Motil KJ, Caeg E, Barrish JO, Geerts S, Lane JB, Percy AK, et al. Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome. *J Pediatr Gastroenterol Nutr* 2012;55(3):292-8.
 - [19] Julu PO, Kerr AM, Apartopoulos F, Al-Rawas S, Engerström IW, Engerström L, et al. Characterisation of breathing and associated central autonomic dysfunction in the Rett disorder. *Arch Dis Child* 2001;85(1):29-37.
 - [20] Glaze DG. Neurophysiology of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002;8(2):66-71.
 - [21] Glaze DG, Schultz RJ. Autonomic dysfunction and sudden death in Rett syndrome: prolonged QTc intervals and diminished heart rate variability. In: Kerr A, Witt Engerström I, editors. Rett disorder and the developing brain. Oxford: Oxford University Press; 2001.p.251-256.
 - [22] Olsson B, Rett A. Behavioural observations concerning differential diagnosis between the Rett syndrome and autism. *Brain Dev* 1985;7(3):281-9.
 - [23] Piaget, J, Inhelder, B. Memory and intelligence. London. Routledge and Kegan Paul; 1973.
 - [24] Lindberg B. Understanding Rett syndrome: a practical guide for parents, teachers, and therapists. Cambridge,MA: Hogrefe & Huber Publishers; 2006. p.50-59.
 - [25] Baptista PM, Mercadante MT, Macedo EC, Schwartzman JS. Cognitive performance in Rett syndrome girls: a pilot study using eyetracking technology. *J Intellect Disabil Res* 2006;50(Pt 9):662-6.

1.2.4 Specific variants of RTT

1.2.4.1 The Preserved Speech Variant (Zappella Variant)

This variant of RTT (Table 1.7 left) was first described in 1992 by Zappella^[1] - which is why it is also called Zappella Variant. The researcher observed three girls who displayed some typical symptoms of RTT (e.g. hand stereotypies) but, at the same time, presented features that were incompatible with the diagnostic criteria for classic RTT. The most prominent of these atypical features was the patients' ability to form full phrases, which is why Zappella proposed the name Preserved Speech Variant (PSV) for this form of RTT^[1]. Equally to classic RTT, the Preserved Speech Variant develops in different stages, although stage II (regression) and stage IV (late deterioration) have been found to have a delayed onset in patients with PSV^[2-5]. Mutations in the *MECP2* gene, which have been identified to cause classic RTT, have been detected in some 50% of the patients. Unlike to classic RTT, in which early truncating mutations are the most common, girls with PSV rather have mutations at the end of the gene^[6,7].

Some typical features of classic RTT such as loss of acquired language and hand skills during the regression period, development of stereotypic hand movements, gait abnormalities and sleep disturbances are also common in individuals with PSV^[1-7]. Autistic behaviours are also frequently observed and in fact, many girls meet the DSM IV criteria for autism^[2,6]. This might contribute to the occasionally reported misdiagnoses with 'infantile autism' or 'autistic disorder'^[2,7]. Other symptoms such as epilepsy, gastrointestinal disturbances, insufficient peripheral circulation and scoliosis have been found to occur less frequently and/or in a milder form^[2,6,7]. The somatic features of patients with PSV also differ from those seen in individuals with classic RTT as microcephaly, microsomia and decreased body weight are rare. In fact, obesity, macrocephaly and tall stature have been reported in some patients with PSV^[6,7]. After the regression period, girls with PSV usually show a slow but constant improvement of hand skills which does not occur in classic RTT. Some females are able to build towers of cubes, write short sentences, make simple drawings or use cutlery to feed themselves^[2,3,6,7].

As mentioned above the ability to produce phrases has been described as the most striking feature in individuals with PSV. However, some studies have report a wide range of the language skills between different patients. Some individuals can only say few words but are unable to combine them while others are able to produce quite complex phrases^[3,6,7]. The level of speech has been found to be correlated to the degree of overall severity. Patients with more restricted language skills tend to be rather small and malnourished while those with more complex abilities usually have normal or even high body mass indexes and better hand function^[6,7]. Additionally, speech is commonly deficient in quality and echolalia, repetitive questioning, stuttering or staccato type speech often occur^[2-4,6,7].

Initially patients with PSV have been thought to develop normally for the first 9 to 36 months of life, although subtle deviations in social interaction have been reported^[1,2]. Yet, by retrospective analysis of home videos of six girls with PSV, Marschik and colleagues^[5] found abnormalities both in motor and vocal development already during early infancy. Unusual inspiratory, pressed or high-pitched crying-like vocalisations were interspersed with typical age-specific patterns. Furthermore, the onset of canonical babbling was frequently delayed or even absent during the observation period. These findings provide clear evidence that, just as classic RTT, the Preserved Speech Variant manifests itself already in the pre-regression period^[3,5].

Recently, the appropriateness of the term 'preserved speech' has been called in question by

some researchers^[4,5,7]. They argued that speech is in fact not preserved as it is completely or partly lost during the regression period. Furthermore, they stressed that the ability to produce words or phrases is not the only feature which distinguishes this variant from classic RTT. Renieri and colleagues thus proposed to relabel this form in Zappella Variant^[7].

1.2.4.2 The Early Seizure Variant (Hanefeld Variant)

This variant of RTT (Table 1.7 middle), first described by Hanefeld in 1985^[8], is characterised by an early onset of seizures which usually occur between the 1st and the 10th week of age. The types of seizures may vary between different patients and include infantile spasms, generalised tonic-clonic seizures, myoclonic seizures, complex partial seizures and tonic seizures. It is worth mentioning that the seizures, regardless of type, were drug resistant in all 39 patients identified with this variant by 2010^[9-17].

Individuals affected by the Early Seizure Variant of RTT further show early and severe impairment of psychomotor development. Many of them never acquire the ability to sit and only a few can walk^[9]. Only 2 out of 39 patients reported by 2010 were able to say a few words^[9-17]. Similar to classic RTT, hand function is often absent or poor and hand stereotypies are constantly present. Yet, contrary to patients with classic RTT, individuals with the Early Seizure Variant usually have normal body weight and height and do not develop scoliosis. Furthermore, deceleration of head circumference occurs less often than in patients with classic RTT and autonomic disturbances are rare^[9]. One of the most striking features of the Early Seizure Variant - apart from the early onset of seizures and the severe deviations in psychomotor development - is the poor eye contact, which, by contrast, has been described as very intense in patients with classic RTT and is even one of the supportive criteria for RTT^[9,18].

Genetic testing has not revealed mutations in the *MECP2* gene in any of the 39 patients with this variant of RTT identified until 2010^[9-17]. However, in 2004 the Early Seizure Variant was, for the first time, associated with mutations in the cyclin-dependent kinase like 5 (*CDKL5*) gene, which is located in Xp22^[16]. Today, genetic testing for mutations in this gene is recommended for patients with clinical features of the Early Seizure Variant^[18].

1.2.4.3 The Congenital Variant (Rolando Variant)

The Congenital Variant of RTT (Table 1.7 right) was first described by Rolando in 1985^[19]

and has been associated with mutations in the *FOXG1* gene since 2008^[20]. The clinical presentation of the patients with this variant differs from that of individuals with classic RTT in the presence of significant developmental deviations already within the first months of life. The patients are mostly affected by hypotonia and unable to acquire important milestones of motor development such as head control, sitting and walking. Microcephaly is often more severe and manifests itself earlier than in classic RTT. Patients with the Congenital Variant also lack the intense eye gaze commonly observed in individuals with the classic RTT. However, similar to classic RTT, breathing abnormalities, hand stereotypies and signs of peripheral vasomotor disturbances such as cold feet have frequently been observed in patients with this variant^[19-24]. Kortüm and colleagues further identified sleep disturbances, seizures and gastroesophageal reflux - symptoms that often occur in classic RTT - in the majority of 11 patients with *FOXG1* mutations^[25]. However, these researchers could not reveal a history of regression in nine patients and for the remaining two a period of subtle regression was reported. Since a history of regression is required for the diagnosis of RTT (both for the classic form as well as for variants)^[18], the apparent lack of regression together with some differences found between classic RTT and this variant led Kortüm and colleagues to assume "that the combination of developmental and brain imaging features observed in individuals with *FOXG1* mutations are sufficiently distinct [to those observed in patients with classic RTT] to allow clinical recognition of this disorder"^[25, p.404].

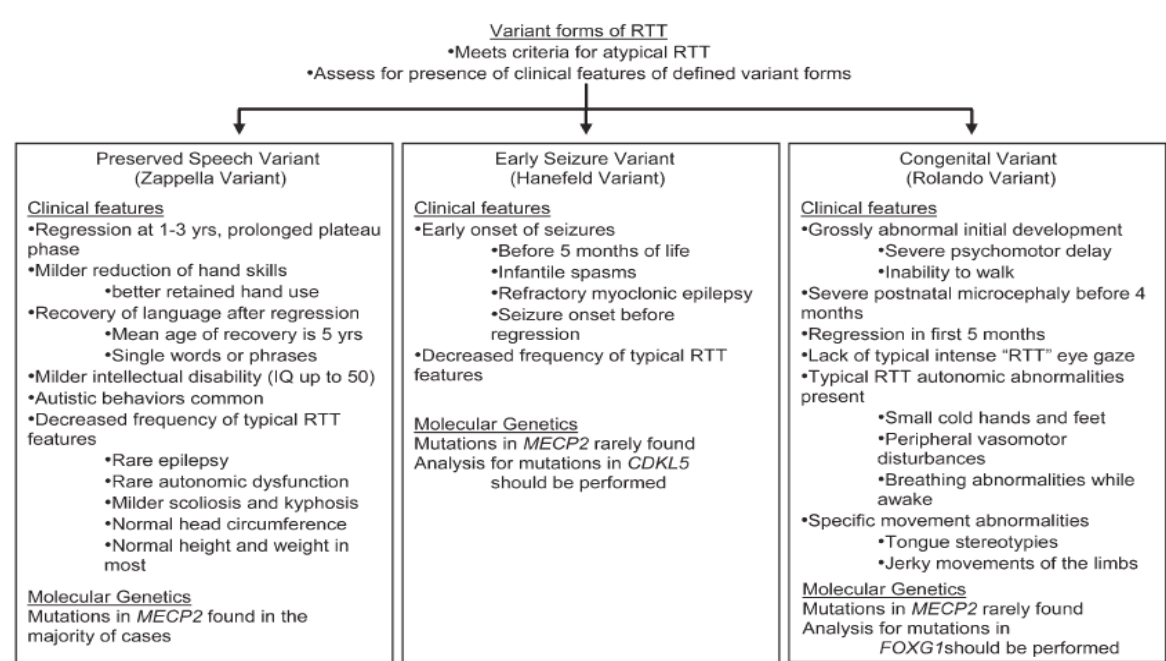


Table 1.7: Clinical features and genetic background for specific variants of RTT^[18]

References for 1.2.4 Specific variants of RTT

- [1] Zappella M. The Rett girls with preserved speech. *Brain Dev* 1992;14(2):98-101.
- [2] Zappella M, Gillberg C, Ehlers S. The preserved speech variant: a subgroup of the Rett complex: a clinical report of 30 cases. *J Autism Dev Disord* 1998;28(6):519-26.
- [3] Marschik PB, Einspieler C, Oberle A, Laccone F, Prechtl HF. Case report: Retracing atypical development: a preserved speech variant of Rett syndrome. *J Autism Dev Disord* 2009;39(6):958-61.
- [4] Marschik PB, Einspieler C, Prechtl HF, Oberle A, Laccone F. Relabelling the preserved speech variant of Rett syndrome?. *Dev Med Child Neurol* 2010;52(2):218.
- [5] Marschik PB, Pini G, Bartl-Pokorny KD, Duckworth M, Gugatschka M, Vollmann R, et al. Early speech-language development in females with Rett syndrome: focusing on the preserved speech variant. *Dev Med Child Neurol* 2012 ;54(5):451-6.
- [6] Zappella M, Meloni I, Longo I, Hayek G, Renieri A. Preserved speech variants of the Rett syndrome: molecular and clinical analysis. *Am J Med Genet* 2001;104(1):14-22.
- [7] Renieri A, Mari F, Mencarelli MA, Scala E, Ariani F, Longo I, et al. Diagnostic criteria for the Zappella variant of Rett syndrome (the preserved speech variant). *Brain Dev* 2009;31(3):208-16.
- [8] Hanefeld F. The clinical pattern of the Rett syndrome. *Brain Dev* 1985;7(3):320-5.
- [9] Artuso R, Mencarelli MA, Polli R, Sartori S, Ariani F, Pollazzon M, et al. Early-onset seizure variant of Rett syndrome: definition of the clinical diagnostic criteria. *Brain Dev* 2010;32(1):17-24.
- [10] Evans JC, Archer HL, Colley JP, Ravn K, Nielsen JB, Kerr A, et al. Early onset seizures and Rett-like features associated with mutations in CDKL5. *Eur J Hum Genet* 2005;13(10):1113-20.
- [11] Tao J, Van Esch H, Hagedorn-Greiwe M, Hoffmann K, Moser B, Raynaud M, et al. Mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5/STK9) gene are associated with severe neurodevelopmental retardation. *Am J Hum Genet* 2004;75(6):1149-54.
- [12] Archer HL, Evans J, Edwards S, Colley J, Newbury-Ecob R, O'Callaghan F, et al. CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients. *J Med Genet* 2006;43(9):729-34.
- [13] Nectoux J, Heron D, Tallot M, Chelly J, Bienvenu T. Maternal origin of a novel C-terminal truncation mutation in CDKL5 causing a severe atypical form of Rett syndrome. *Clin Genet* 2006;70(1):29-33.
- [14] Rosas-Vargas H, Bahi-Buisson N, Philippe C, Nectoux J, Girard B, N'Guyen Morel MA, et al. Impairment of CDKL5 nuclear localisation as a cause for severe infantile encephalopathy. *J Med Genet* 2008;45(3):172-8.
- [15] Pintaudi M, Baglietto MG, Gaggero R, Parodi E, Pessagno A, Marchi M, et al. Clinical and electroencephalographic features in patients with CDKL5 mutations: two new Italian cases and review of the literature. *Epilepsy Behav* 2008;12(2):326-31.
- [16] Weaving LS, Christodoulou J, Williamson SL, Friend KL, McKenzie OL, Archer H, et al. Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. *Am J Hum Genet* 2004;75(6):1079-93.
- [17] Bahi-Buisson N, Kaminska A, Boddaert N, Rio M, Afenjar A, Gérard M, Giuliano et al. The three stages of epilepsy in patients with CDKL5 mutations. *Epilepsia* 2008;49(6):1027-37.
- [18] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;68(6):944-50.
- [19] Rolando S. Rett syndrome: report of eight cases. *Brain Dev* 1985;7(3):290-6.
- [20] Ariani F, Hayek G, Rondinella D, Artuso R, Mencarelli MA, Spanhol-Rosseto A, et al. FOXP1 is responsible for the congenital variant of Rett syndrome. *Am J Hum Genet* 2008;83(1):89-93.
- [21] Bahi-Buisson N, Nectoux J, Girard B, Van Esch H, De Ravel T, Boddaert N, et al. Revisiting the phenotype associated with FOXP1 mutations: two novel cases of congenital Rett variant. *Neurogenetics* 2010;11(2):241-9.
- [22] Mencarelli MA, Spanhol-Rosseto A, Artuso R, Rondinella D, De Filippis R, Bahi-Buisson N, et al. Novel FOXP1 mutations associated with the congenital variant of Rett syndrome. *J Med Genet* 2010;47(1):49-53.
- [23] Philippe C, Amsallem D, Francannet C, Lambert L, Saunier A, Verneau F, et al. Phenotypic variability in Rett syndrome associated with FOXP1 mutations in females. *J Med Genet* 2010;47(1):59-65.
- [24] Le Guen T, Bahi-Buisson N, Nectoux J, Boddaert N, Fichou Y, Diebold B, et al. A FOXP1 mutation in a boy with congenital variant of Rett syndrome. *Neurogenetics* 2011;12(1):1-8.
- [25] Kortüm F, Das S, Flindt M, Morris-Rosendahl DJ, Stefanova I, Goldstein A, et al. The core FOXP1 syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis. *J Med Genet* 2011;48(6):396-406.

1.3 Pathophysiology of RTT

1.3.1 Genetic background

1.3.1.1 The methyl-CpG-binding protein 2

The methyl-CpG-binding protein 2 (MeCP2) is encoded by the MECP2 gene, which is located at the end of the long arm of the X chromosome - locus Xq28 - and undergoes X-inactivation^[1,2]. The gene consists of 4 exons and, so far, two splice variants - MeCP2_e1 and MeCP2_e2 - have been identified. The only difference between the two isoforms is the N-terminus, as MeCP2_e1 is translated from exons 1, 3 and 4 and lacks the amino acids of exon 2, whereas the MeCP2_e2 isoform has its translational start in exon 2 (Figure 1.6). The expression levels of MeCP2_e1 in the brain have been found to be ten times than those for MeCP2_e2^[3].

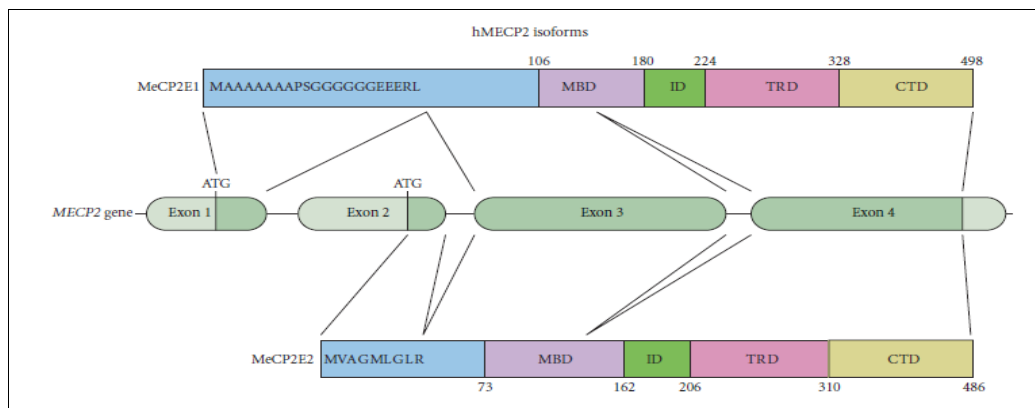


Figure 1.6: Illustration of the structure of MECP2 and the different domains of the two protein isoforms, MeCP2_e1 and MeCP2_e2^[25].

MeCP2 is part of the MBD protein family which bind to methylated DNA. DNA methylation is known to be an important factor in epigenetic regulation and is often associated with transcriptional repression^[4,5]. Thus, it is not surprising that MeCP2 has been found to function as a repressor of gene transcription. The protein binds to methylated cytosine residues via its methyl-binding-domain (MBD), one of the two main functional domains of MeCP2. The second domain, the transcription-repression-domain interacts with co-repressor complex Sin3A to recruit the histone deacetylases 1 and 2 (HDAC1 and HDAC2) and form compact chromatin structures which are inaccessible for transcription^[6-9].

However, a recent study suggested that MeCP2 also functions as activator of transcription.

Analysing gene expression in the hypothalamus of both mice lacking and overexpressing *Mecp2*, Chahour and colleagues found that of the 2582 genes misregulated in both models, 85% were downregulated and only 377 genes were upregulated in *Mecp2*-null mice. The high amount of downregulated genes makes secondary changes as underlying process for transcriptional repression in *Mecp2*-null mice unlikely. Further analysis revealed a binding of MeCP2 to several activated genes in association with the transcriptional activator CREB1^[10].

MeCP2 is expressed in many tissues including the lung, the heart and several organs of the gastrointestinal tract^[1,2]. Yet, the highest levels of the protein have been found in the brain, especially in postmitotic neurons. Several researchers revealed that the expression patterns of MeCP2 follow that of neuronal maturation. The protein can first be detected in the early developing structures such as the spinal cord and the brainstem. Regarding the cortex, the Cajal-Retzius cells, which are the first to originate from the ventricular zone are also the first to express MeCP2. Next, MeCP2 can be detected in the deep cortical layers, whereas the superficial cortical layers, which contain the latest developing neurons also show a later onset of MeCP2 expression^[11-13]. The number of neurons expressing the protein also varies between different brain regions. Shahbazian and colleagues found that the reticular formation of the brainstem did not show a major increase of MeCP2 expressing neurons between late gestation and 10 years of age in humans, whereas the number of cortical neurons with detected MeCP2 levels increased from 10% at 26 weeks of gestation to 80% at 10 years of age. According to the researchers, this reflects the preference of MeCP2 expression in mature neurons and the "extended period of developmental [experience-dependent] plasticity in humans, in which neurons have not achieved their fully differentiated state"^[11, p.119].

MeCP2 was initially thought to be absent in glia, yet recently, Ballas and colleagues detected MeCP2 expression in astrocytes^[14]. Furthermore, MeCP2 has been found to be present not only in the nucleus of neurons but also in the postsynaptic compartment, which suggests an involvement of MeCP2 in synaptic activity^[15]. Cohen and colleagues revealed that MeCP2 is present in olfactory epithelium before synaptogenesis and that, at the same time, expression levels of MeCP2 were decreased if synaptogenesis was blocked by axotomy^[16]. Considering these results, some researchers suggest that MeCP2 expression might be initiated by cell-autonomous mechanisms, but that the increase of expression might be mediated through non-cell-autonomous effects such as stimulation from other

neurons^[17,18].

Though a large number of misregulated genes have been found in *Mecp2*-null mice, only few of them have so far been identified as a direct target of MeCP2 (Table 1.8, p.46). Some of the proteins encoded by these genes are important for the development and function of the CNS. *BDNF*, for example, encodes for the brain derived neurotrophic factor, which is especially active in the hippocampus, the cortex and the basal forebrain. The protein induces neuronal growth and differentiation and is important for the generation of synapses^[19]. The expression of BDNF has recently been found to be induced by activity-dependent phosphorylation of MeCP2 which leads to a dissociation of the protein from the BDNF promotor III and thus, relieves the repression of transcription^[20]. *A2BP1* encodes for the ataxin 2 binding protein 1, which regulates neuronal gene splicing and has occasionally been associated with cognitive impairment, autism and epilepsy^[21,22]. Deficits of guanidinoacetate methyltransferase, encoded by *GAMT*, have been found in patients with absent speech development, seizures, hypotonia and severe cognitive impairment^[23,24].

1.3.1.2 Mutations in the *MECP2* gene in RTT

Due to its almost complete restriction to females, RTT has been proposed as a X-linked dominant, male lethal (XDML) disorder since its first widespread recognition^[26]. Some boys with a classic RTT phenotype have been described, but they had either somatic mosaicism or Klinefelter Syndrome^[27,28]. In familial cases of RTT, male descendants are often affected by a severe neonatal encephalopathy and die during infancy^[29]. Though RTT has early been linked to the X chromosome, it was not before 1999 that a team at Baylor College of Medicine discovered *MECP2* as causative gene for RTT. They found *de novo* mutations - either in the MBD or in the TRD - in five out of 21 sporadic patients and 2 identical mutations in a half-sister pair^[30].

Familial cases of RTT, in which more than one daughter is affected, are rare and account for less than 1% of all RTT cases. Thus, it was soon supposed that *MECP2* was very vulnerable to mutation and that most of the mutations occur sporadically^[31]. This assumption was further supported by Fyve and colleagues, who found no increase of miscarriages of male foetuses in families with a single affected daughter, which would be expected in a directly transmitted XDML disorder^[32]. The inheritance of RTT in familial cases with an apparently healthy mother was explained as result of a favourable skewed X-inactivation pattern of the mother^[31]. One severely affected family with a healthy mother

Gene target	Function	Cell/tissue type studied	Direct association with MeCP2 (cell line used for ChIP)
<i>PCDHB1</i>	Cell adhesion	Oral cancer cell lines (ZA, KOSC2, HSC5, NA)	Yes (SH-SY5Y)
<i>PCDH7</i>	Cell adhesion		Yes (SH-SY5Y)
<i>APBP3</i>	Intracellular signal transduction		Yes (SH-SY5Y)
<i>CLU</i>	Extracellular molecular chaperone	RTT patient brain (frontal cortex)	No (SH-SY5Y)
<i>CRMP1</i>	Component of semaphoring signal transduction pathway		Yes (SH-SY5Y)
<i>DNMI</i>	Vesicular trafficking, production of microtubule bundles, hydrolyzes GTP		Yes (SH-SY5Y)
<i>GNBI</i>	Integrates signals between receptor and effector proteins		Yes (SH-SY5Y)
<i>APLP1</i>	Enhancer of neuronal apoptosis		No (SH-SY5Y)
<i>CO1</i>	Mitochondrial respiratory chain		No (SH-SY5Y)
<i>GDI1</i>	Regulates GDP/GTP exchange		No (SH-SY5Y)
<i>Bdnf</i>	Neuronal plasticity and survival	Mouse E14 cortical culture Rat E18 cortical neurons	Yes (mouse E14 cortical culture Rat E18 cortical Neurons)
<i>Fxyd1</i>	Ion transport regulator for Na, K-ATPase	RTT mice cerebellum RTT patient's brain—superior frontal gyrus	Yes (adult mice brain, <i>Mecp2</i> wt and <i>Mecp2</i> null mouse; HEK293T cells)
<i>Reln</i> <i>Gtl2</i>	Neuronal layer formation, cell-cell interactions Growth suppressor	RTT mice cerebellum	Yes (adult mice brain)
<i>ID1</i> <i>ID2</i> <i>ID3</i> <i>ID4</i>	Regulation of neuronal differentiation	SH-SY5Y	Yes (SH-SY5Y)
<i>IGFBP3</i>	Modulation of IGF functions	RTT mice model	Yes (HeLa cells; mice cortices)
<i>UBE3A</i> <i>GABRB3</i>	Ubiquitin ligase GABA-A receptor	Brain cerebral samples of RTT, AS, and autism patients	No (adult mouse cerebellum samples)
<i>Sst</i> <i>Oprk1</i> <i>Gamt</i> <i>Gprin1</i> <i>Mef2c</i> <i>A2bp1</i>	Regulation of cell migration Signal transduction Organ morphogenesis Neurite development Neuron development and differentiation RNA splicing and mRNA processing	RTT mice models (<i>Mecp2</i> null and <i>Mecp2</i> Tg) and control mice; Hypothalamus	Yes (RTT mice models (<i>Mecp2</i> null and <i>Mecp2</i> Tg) and control mice; Hypothalamus)
<i>xHairy2a</i>	Neuronal differentiation	Xenopus embryos	Yes (xenopus neurula stage embryos)
<i>Sgk1</i> <i>Fkbp5</i>	Cellular stress response Hormone signalling	RTT mice model; brain samples	Yes (mice brain tissue)
<i>Uqcrc1</i>	Mitochondrial respiratory chain	RTT mice model; brain samples	Yes (adult mice; whole brain)
<i>Crh</i>	Stress response	RTT mice model; brain samples	Yes (RTT mice brain samples)
<i>Dlx5</i>	Transcription factor	Not done	Yes (mouse brain)

Table 1.8: Known targets of MeCP2[25], with permission.

was found in Brazil. Three daughters are affected by RTT, two other daughters died at 9 months respectively at 3 years of age and the single male descendant died at 3 days of age (Figure 1.7). The X-inactivation pattern of the mother has been found to be extremely favourable, as the unmutated X chromosome was dominant in 95% of her cells. This family case, studied by Sirianni and colleagues in 1998, led to the approval of an X-linked inheritance and the mapping of the mutated gene at Xq28^[33].

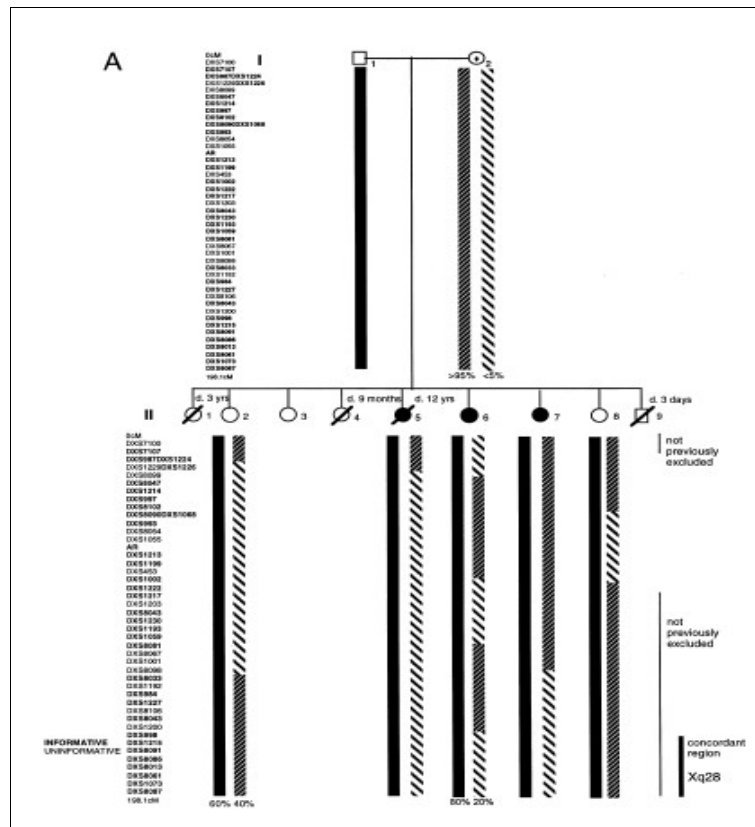


Figure 1.7: Pedigree of a Brazilian family case of RTT. Three daughters are affected by RTT. Two apparently healthy daughters died at 9 months and 3 years respectively. The only male descendant died at 3 days postnatal. Note the extremely skewed X-inactivation of the mother (>95%:<5%). Genetic analysis of the family members revealed that only the Xq28 region was concordant in the affected daughters[2].

Although the fact that surviving males in RTT families are severely affected and die early supports the hypothesis of RTT as an XDML disorder, another model of inheritance was suggested by some researchers. They found that mutations in the *MECP2* gene occurred mostly in the paternal germ cell line, which might be prone to mutation due to the higher CpG methylation state when compared to female germ cell lines. Consequently, male descendants would be excluded from the disorder as they don't inherit the affected X chromosome. In familial cases as well as in rare sporadic male cases, a defect on the maternal X chromosome would be responsible for the severe phenotype in males due to their absence of a second, protective X-chromosome^[34,35]. Due to their severe disability, intentional sexual reproduction of women with RTT has never been observed and only one case of transmission from an affected woman to her daughter, in which the conception occurred as a result of sexual abuse, has been reported^[36].

Though Amir and colleagues found mutations in the *MECP2* gene in only about 24% of their 29 study participants, the usage of more advanced methods and the increase of mutation testing of affected women has led to the detection of *MECP2* mutations in over

95% of girls and women with classic RTT and in about 30% of girls and women with RTT variants^[37,38].

Research focussing on the different locations of mutations within the *MECP2* gene has resulted in the discovery of over 200 mutations until now. They are distributed along the whole gene and include various types, although the most common are missense, nonsense and frameshift mutations. Missense mutation, resulting in a dysfunctional protein, are rather detected in the MBD or at the final part of the TRD, whereas truncating mutations - nonsense or frameshift mutations which lead to an early stop of the transcription - more often affect the sequences between the MBD and the initial part of the TRD. Of these 200 mutations, the eight most recurrent mutations account for more than 65% of all mutation positive RTT cases. All of them are characterised by a cytosine to thymine transition^[39]. Lima and colleagues revealed that 88.1% of all *MECP2* mutations in their 74 patients were cytosine to thymine transitions at CpG islands^[40]. The C-terminus of the gene has been found to be a "hot spot for deletions"^[39, p.734], which account for about 10% of all mutation positive RTT cases. Only rarely, mutations have been detected in the N-terminus of the gene, but the possibility should still be considered, especially if earlier analyses could not reveal any mutation in a patient with RTT^[39].

References for 1.3.1 Genetic background

- [1] D'Esposito M, Quaderi NA, Ciccodicola A, Bruni P, Esposito T, D'Urso M, Brown SD. Isolation, physical mapping, and northern analysis of the X-linked human gene encoding methyl-CpG-binding protein, MECP2. *Mamm Genome* 1996;7(7):533-5.
- [2] Sirianni N, Naidu S, Pereira J, Pillotto RF, Hoffman EP. Rett syndrome: confirmation of X-linked dominant inheritance, and localization of the gene to Xq28. *Am J Hum Genet* 1998;63(5):1552-8.
- [3] Kriaucionis S, Bird A. The major form of MeCP2 has a novel N-terminus generated by alternative splicing. *Nucleic Acids Res* 2004;32(5):1818-23.
- [4] Song F, Smith JF, Kimura MT, Morrow AD, Matsuyama T, Nagase H, et al. Association of tissue-specific differentially methylated regions (TDMs) with differential gene expression. *Proc Natl Acad Sci U S A* 2005;102(9):3336-41.
- [5] Reik W, Collick A, Norris ML, Barton SC, Surani MA. Genomic imprinting determines methylation of parental alleles in transgenic mice. *Nature* 1987;328(6127):248-51.
- [6] Meehan RR, Lewis JD, Bird AP. Characterization of MeCP2, a vertebrate DNA binding protein with affinity for methylated DNA. *Nucleic Acids Res* 1992;20(19):5085-92.
- [7] Lewis JD, Meehan RR, Henzel WJ, Maurer-Fogy I, Jeppesen P, Klein F, et al. Purification, sequence, and cellular localization of a novel chromosomal protein that binds to methylated DNA. *Cell* 1992;69(6):905-14.
- [8] Nan X, Ng HH, Johnson CA, Laherty CD, Turner BM, Eisenman RN, et al. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. *Nature* 1998;393(6683):386-9.
- [9] Jones PL, Veenstra GJ, Wade PA, Vermaak D, Kass SU, Landsberger N, et al. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. *Nat Genet* 1998;19(2):187-91.
- [10] Chahrour M, Jung SY, Shaw C, Zhou X, Wong ST, Qin J, et al. MeCP2, a key contributor to neurological disease, activates and represses transcription. *Science* 2008;320(5880):1224-9.
- [11] Shahbazian MD, Antalffy B, Armstrong DL, Zoghbi HY. Insight into Rett syndrome: MeCP2 levels display tissue- and cell-specific differences and correlate with neuronal maturation. *Hum Mol Genet* 2002;11(2):115-24.
- [12] Marin-Padilla M. Cajal-Retzius cells and the development of the neocortex. *Trends Neurosci* 1998;21(2):64-71.
- [13] Jacobson M. *Developmental Neurobiology*, 3rd edition. New York: Plenum Press; 1998.
- [14] Ballas N, Lioy DT, Grunseich C, Mandel G. Non-cell autonomous influence of MeCP2-deficient glia on neuronal dendritic morphology. *Nat Neurosci* 2009;12(3):311-7.

- [15] Aber KM, Nori P, MacDonald SM, Bibat G, Jarrar MH, Kaufmann WE. Methyl-CpG-binding protein 2 is localized in the postsynaptic compartment: an immunochemical study of subcellular fractions. *Neuroscience* 2003;116(1):77-80.
- [16] Cohen DR, Matarazzo V, Palmer AM, Tu Y, Jeon OH, Pevsner J, et al. Expression of MeCP2 in olfactory receptor neurons is developmentally regulated and occurs before synaptogenesis. *Mol Cell Neurosci* 2003;22(4):417-29.
- [17] LaSalle JM, Goldstine J, Balmer D, Greco CM. Quantitative localization of heterogeneous methyl-CpG-binding protein 2 (MeCP2) expression phenotypes in normal and Rett syndrome brain by laser scanning cytometry. *Hum Mol Genet* 2001;10(17):1729-40.
- [18] Armstrong DD. Neuropathology of Rett syndrome. *J Child Neurol* 2005;20(9):747-53.
- [19] Huang EJ, Reichardt LF. Neurotrophins: Roles in Neuronal Development and Function. *Annu Rev Neurosci* 2001;24: 677-736.
- [20] Zhou Z, Hong EJ, Cohen S, Zhao WN, Ho HY, Schmidt L, et al. Brain-specific phosphorylation of MeCP2 regulates activity-dependent Bdnf transcription, dendritic growth, and spine maturation. *Neuron* 2006;52(2):255-69.
- [21] Bhalla K, Phillips HA, Crawford J, McKenzie OL, Mulley JC, Eyre H, et al. The de novo chromosome 16 translocations of two patients with abnormal phenotypes (mental retardation and epilepsy) disrupt the A2BP1 gene. *J Hum Genet* 2004;49(6):308-11.
- [22] Martin CL, Duvall JA, Ilkin Y, Simon JS, Arreaza MG, Wilkes K, et al. Cytogenetic and molecular characterization of A2BP1/FOX1 as a candidate gene for autism. *Am J Med Genet B Neuropsychiatr Genet* 2007;144B(7):869-76.
- [23] Caldeira Araújo H, Smit W, Verhoeven NM, Salomons GS, Silva S, Vasconcelos R, et al. Guanidinoacetate methyltransferase deficiency identified in adults and a child with mental retardation. *Am J Med Genet A* 2005;133A(2):122-7.
- [24] Verbruggen KT, Knijff WA, Soorani-Lunsing RJ, Sijens PE, Verhoeven NM, Salomons GS, et al. Global developmental delay in guanidinoacetate methyltransferase deficiency: differences in formal testing and clinical observation. *Eur J Pediatr* 2007;166(9):921-5.
- [25] Zachariah RM, Rastegar M. Linking epigenetics to human disease and Rett syndrome: the emerging novel and challenging concepts in MeCP2 research. *Neural Plast* 2012;2012:415825.
- [26] Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol* 1983;14(4):471-9.
- [27] Topçu M, Akyerli C, Sayi A, Törüner GA, Koçoğlu SR, Cimbış M, et al. Somatic mosaicism for a MECP2 mutation associated with classic Rett syndrome in a boy. *Eur J Hum Genet* 2002;10(1):77-81.
- [28] Schwartzman JS, Bernardino A, Nishimura A, Gomes RR, Zatz M. Rett syndrome in a boy with a 47,XXY karyotype confirmed by a rare mutation in the MECP2 gene. *Neuropediatrics* 2001;32(3):162-4.
- [29] Schanen NC, Kurczynski TW, Brunelle D, Woodcock MM, Dure LS 4th, Percy AK. Neonatal encephalopathy in two boys in families with recurrent Rett syndrome. *J Child Neurol* 1998;13(5):229-31.
- [30] Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;23(2):185-8.
- [31] Clarke A, Schanen C, Anvret M. Towards the genetic basis of Rett syndrome. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.27-56.
- [32] Fyfe S, Leonard H, Dye D, Leonard S. Patterns of pregnancy loss, perinatal mortality, and postneonatal childhood deaths in families of girls with Rett syndrome. *J Child Neurol* 1999;14:440-5.
- [33] Sirianni N, Naidu S, Pereira J, Pillotto RF, Hoffman P. Rett syndrome: confirmation of X-linked dominant inheritance, and localization of the gene to Xq28. *Am J Hum Genet* 1998;63(5):1552-8.
- [34] Trappe R, Laccone F, Cobilanschi J, Meins M, Huppke P, Hanefeld F, et al. MECP2 mutations in sporadic cases of Rett syndrome are almost exclusively of paternal origin. *Am J Hum Genet* 2001;68(5):1093-101.
- [35] Girard M, Couvert P, Carrié A, Tardieu M, Chelly J, Beldjord C, et al. Parental origin of de novo MECP2 mutations in Rett syndrome. *Eur J Hum Genet* 2001;9(3):231-6.
- [36] Engerström IW, Forslund M. Mother and daughter with Rett Syndrome. *Dev Med Child Neurol* 1992;34(11):1022-3.
- [37] Amir R, Sutton V, Van den Veyver I. Newborn screening and prenatal diagnosis for Rett syndrome: implications for therapy. *J Child Neurol* 2005;20:779- 83.
- [38] Temudo T, Santos M, Ramos E, Dias K, Vieira JP, Moreira A, et al. Rett syndrome with and without detected MECP2 mutations: an attempt to redefine phenotypes. *Brain Dev* 2011;33(1):69-76.
- [39] Huppke P, Gärtner J. Molecular diagnosis of Rett syndrome. *J Child Neurol* 2005;20(9):732-6.
- [40] Lima FT, Brunoni D, Schwartzman JS, Pozzi MC, Kok F, Juliano Y, et al. Genotype-phenotype correlation in Brazilian Rett syndrome patients. *Arq Neuropsiquiatr* 2009;67(3A):577-84.

1.3.2 Central nervous system malfunction in RTT

1.3.2.1 Neuropathology

Although the gross appearance of the RTT patients' brain corresponds to that of a normal brain, several neuroimaging and autopsy studies have revealed a variety of structural abnormalities^[1-5]. Furthermore, the brain of patients with RTT has been found to be reduced in size and weight. A comparison of the brain weights of 51 females with RTT revealed a mean brain weight of 993g, which corresponds to that of a 1-year-old child. In the sample, there was no decrease of brain weight with age^[6]. Neuroimaging studies showed that the prefrontal, posterior frontal and anterior temporal regions were especially affected by volumetric decline^[7], while the occipital region seemed to be mainly spared from this phenomenon^[4,7-9]. Carter and colleagues further revealed significant volumetric reductions in the parietal lobe in 23 girls with confirmed *MECP2* mutation^[8]. Though some researchers stated that grey matter (GM) and white matter (WM) were equally affected^[2], others revealed a greater involvement of GM^[4,8,9]. A common finding was that the reduction of brain tissue was not progressive which, together with the above mentioned lack of brain weight decrease with age, contradicts the initial hypothesis that RTT was a progressive degenerative disorder^[4,8-10].

Though Belichenko and colleagues revealed a decline in the number of neurons in the layers II and III in the temporal and frontal cortex^[11], the main causes for the decreased brain size in RTT seem to be a reduction of neuronal soma size and increased packing density as described by Baumann and colleagues as well as a decreased size of minicolumns as described by Casanova and colleagues^[5,13]. Baumann and colleagues revealed a reduced size of neurons in the cortex, the thalamus, the basal ganglia, the amygdala and the hippocampus and an increased packing density in the hippocampus and the entorhinal cortex of patients with RTT^[5]. Relating increased packing density to a deficit of dendritic arborisation, Armstrong and colleagues analysed the dendritic branching of pyramidal neurons in several cortical areas. They revealed that dendritic arborisation was significantly decreased in layers III and V in frontal, motor and temporal cortex but not in the occipital region^[7]. Belichenko and colleagues further described a decreased number and density of dendritic spines, which are essential for the formation of synapses, and abnormalities in the afferent axons which targeted the spines^[13].

1.3.2.2 Pathomechanism of neuronal defects in RTT

Several studies tried to investigate how deficiency of MeCP2 can lead to these abnormalities in the brain in RTT patients. Although the exact mechanism is not fully understood, it has been found that MeCP2 deficiency affects neurons both via cell-autonomous and non-cell-autonomous pathways.

Cell-autonomous effects of MeCP2 deficiency

Squillaro and colleagues analysed bone marrow-derived mesenchymal stem cells (MSCs) from patients with RTT as well as neuroblastoma cells with silenced *MECP2* after inducing neuronal differentiation^[14]. Although MeCP2 has been suggested to be important for the differentiation of post-mitotic neurons rather than cell fate^[15], the researchers revealed increased senescence and an arrest of proliferation in neural precursor cells. A higher percentage of senescent cells was also found in committed and neuron-like cell populations with MeCP2 deficiency when compared to control populations. Thus, the authors concluded that "neural cell fate decisions and neuronal maintenance may be perturbed by the senescence triggered by impaired MeCP2 activity either before or after neural differentiation"^[14, p.1443]. Marchetto and colleagues used pluripotent stem cells from RTT patients to induce neuronal differentiation and found, that the resulting neurons showed a decrease in glutamatergic synapses, spine density and soma size^[16].

Furthermore, differentiated neuron-like cells from RTT patients expressed less neuron-specific enolase (NSE) and microtubule-associated protein 2 (MAP2) than those from healthy controls^[14]. MAP2 is essential for the stabilisation of dendrites and a lack of the protein leads to a reduction in dendritic length in mice^[17]. In RTT, it has been found to be absent in the subplate neurons which, according to Armstrong, might contribute to the abnormal formation of minicolumns in the cortex^[12,18,19].

The pathological findings in the brain of RTT patients and mutant mice have been thought to be caused by abnormalities in the development of the brain. Yet, recently MeCP2 has also been identified to be critical for the maintenance of adult neuronal function. McGraw and colleagues deleted *Mecp2* in fully mature mice and revealed that they developed similar symptoms as those found in germline null mice. The mutant adult mice showed abnormal gait, hind-limb clasping, less activity and deficits in learning^[20]. Another research team tried to investigate the effects of *Mecp2* deletion in both late juvenile (5 weeks old) and adult (10 weeks old) mice. They found that, even though the two types of mice were at

different stages of brain maturation, both types developed RTT-like symptoms with no significant differences in the kinetics of progression or survival rate, which suggests that MeCP2 is required both in the developing and in the adult brain. Analysing the brain of the symptomatic mice the scientists found a reduction of brain size of about 10% when compared to same-aged controls. Interestingly, the brain of the juvenile group at adult age (24 weeks old) was even smaller than that of wild-type mice at 5 weeks of age, suggesting shrinkage of the brain. On morphological level, the researchers identified a variety of features which have earlier been found in RTT patients' brains (see chapter 1.3.2 CNS malfunction in RTT). They found an increased cell density and smaller neuron cell bodies in the hippocampus and the cortex. Furthermore the neurons of the symptomatic mice showed decreased dendritic branching with swelling and thickening of the branches and a reduction of spine density^[21](Figure 1.10).

Non-cell-autonomous effects of MeCP2 deficiency

Some researchers revealed that even "healthy" neurons (neurons with normal MeCP2 expression) were effected by an overall lack of MeCP2. Kishi and Macklis transplanted wild-type neurons into the brains of *Mecp2*-null mice and revealed that these neurons also displayed abnormalities in dendritic arborisation after transplantation^[22] (Figure 1.8). Due to X-inactivation, females with *MECP2* mutations have a certain amount of normal, MeCP2-expressing neurons. Yet, studies on female *Mecp2*-mutant mice have demonstrated that even these *Mecp2*-expressing neurons show decreased dendritic arborisation^[23]. These abnormalities in normal, *Mecp2*-expressing neurons have partly been explained by the involvement of glia, neurotrophic factors and neurotransmitters.

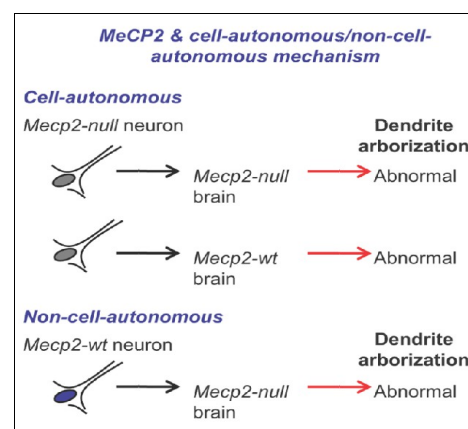


Figure 1.8: Cell-autonomous and non-cell-autonomous effects of MeCP2 on neurons: Examples of transplant experiments^[37].

Effect of mutant glia on neurons

After detecting MeCP2 in astrocytes, Ballas and colleagues studied the effect of mutant astrocytes on surrounding neurons. They revealed that astrocytes with MeCP2 deficiency seem to produce toxic factors that lead to shorter dendrites and early cell death in neurons. Furthermore, the toxic factor seems to be dominant as it led to the above mentioned abnormalities even in mixed cultured media from wild-type and mutant astrocytes^[24] (Figure 1.9).

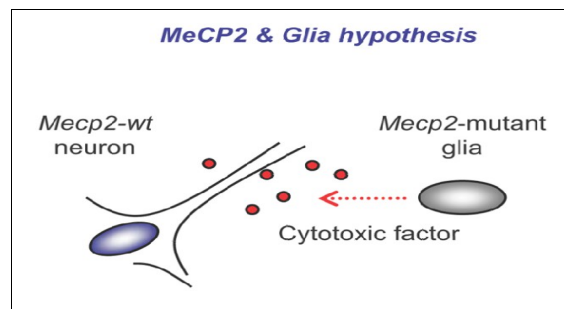


Figure 1.9: Mutant glia may to produce cytotoxic factors which affect wild-type neurons[37].

Abnormal levels of trophic factors

Alterations in some trophic factors have also been found in RTT. Nerve growth factor (NGF), which is essential for the function of cholinergic neurons in the basal forebrain, has been revealed to be decreased in the CSF and in postmortem tissue of the basal forebrain^[25,26]. Chen and colleagues revealed that the transcription of *BDNF* (brain derived neurotrophic factor) was affected by MeCP2 deletion only if there was no neuronal activity while its activity-dependent transcription was equal in wild-type and MeCP2-deficient neurons^[27]. The results of studies on BDNF levels in the brains of mutant mice have been contradictory. Kaufmann and colleagues suggested an overexpression of BDNF in the lack of *Mecn2*; yet, Vermehren-Schmaedick and colleagues found no differences of brainstem BDNF levels between wild-type and *Mecn2*-null mice under normal circumstances and some researchers even revealed decreased levels of the protein in the brain of mutant mice^[28,29,30]. Chang and colleagues suggested that the low BDNF levels were a result of decreased activity-dependent transcription due to reduced cortical activity found in the brain of mutant mice^[30,31]. They revealed that deletion of BDNF from the brain of mutant mice led to an earlier onset and a rapid progression of the disease, whereas overexpression of BDNF decelerated the time of onset and the symptom progression, which supports the

assumption that BDNF is usually reduced in the RTT brain^[30].

Alterations in neurotransmitter levels

Several studies indicate a relation between synaptic activity and normal MeCP2 function. As described in chapter 1.3.1.1 (The methyl-CpG-binding protein 2), MeCP2 levels decrease in the absence of synaptic activity and the transcription of some genes (e.g. *BDNF*) requires the activity-dependent phosphorylation of MeCP2. In patients with RTT, this synaptic activity seems to be impaired and the levels of various neurotransmitters and their receptors have been found to be altered. Several authors described abnormal neurotransmitter levels in the cerebrospinal fluid (CSF) of RTT patients^[32-34]. One of these is glutamate, an excitatory neurotransmitter, which has been revealed to be elevated in the CSF of young individuals with RTT^[32]. Analysing postmortem brain tissue of nine patients with RTT, Blue and colleagues found increased density of ionotropic glutamate receptors in the basal ganglia and increased density of metabotropic glutamate receptors in the prefrontal cortex in young patients. In contrast, all these receptors were decreased in the brain samples of older individuals with RTT. The researchers further revealed that the receptors of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, followed a similar, age-related pattern, as the density of GABA receptors was increased in young and decreased in older patients both in the basal ganglia and the prefrontal cortex^[35]. Measurements of the levels of the dopamine metabolite homovanillic acid (HVA) and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the CSF of RTT patients have led to contradictory results. While some researchers found decreased levels of both the dopamine and the serotonin metabolites, others could not identify any changes^[34,36]. Temudo and colleagues analysed 5-HIAA and HVA levels in the CSF of 25 patients with detected *MECP2* mutations. They found decreased levels of 5-HIAA in some patients and low HVA levels in one. Interestingly, three patients with a p.R294X mutation, who displayed motoric agitation and a variety of stereotypies, had increased levels of HVA^[33].

References for 1.3.2 Central nervous system malfunction in RTT

- [1] Naidu S, Kaufmann WE, Abrams MT, Pearlson GD, Lanham DC, Fredericksen KA, et al. Neuroimaging studies in Rett syndrome. *Brain Dev.* 2001 Dec;23 Suppl 1:S62-71.
- [2] Abrams MT, Mazur-Hopkins P, Pearlson GD, Kaufmann WE, Naidu S. Brain MRI changes in Rett syndrome: cross-sectional and serial data. *Soc Neurosci* 1999;25:488a.
- [3] Kaufmann WE, Pearlson GD, Naidu S. The neuroanatomy of Rett syndrome: neuropathological and neuroimaging studies. *Rivista Medica* 1998;4(4):187-199.
- [4] Reiss AL, Faruque F, Naidu S, Abrams M, Beaty T, Bryan RN, et al. Neuroanatomy of Rett syndrome: a volumetric imaging study. *Ann Neurol* 1993;34:227-234.
- [5] Bauman ML, Kemper TL, Arin DM. Microscopic observations of the brain in Rett syndrome.

- Neuropediatrics 1995;26(2):105-8.
- [6] Armstrong DD, Kinney HC. The neuropathology of the Rett disorder. In: Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. Rett disorder and the developing brain. Oxford: Oxford University Press; 2001. p.57-84.
 - [7] Armstrong D, Dunn JK, Antalffy B, Trivedi R. Selective dendritic alterations in the cortex of Rett syndrome. *J Neuropathol Exp Neurol* 1995;54(2):195-201.
 - [8] Carter JC, Lanham DC. Selective cerebral volume reduction in Rett syndrome: a multiple-approach MR imaging study. *AJNR Am J Neuroradiol* 2008;29(3):436-41.
 - [9] Subramaniam B, Naidu S, Reiss AL. Neuroanatomy in Rett syndrome: cerebral cortex and posterior fossa. *Neurology* 1997;48(2):399-407.
 - [10] Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol* 1983;14(4):471-9.
 - [11] Belichenko PV, Hagberg B, Dahlström A. Morphological study of neocortical areas in Rett syndrome. *Acta Neuropathol* 1997;93(1):50-61.
 - [12] Casanova MF, Buxhoeveden D, Switala A, Roy E. Rett syndrome as a minicolumnopathy. *Clin Neuropathol* 2003;22(4):163-8.
 - [13] Belichenko PV, Oldfors A, Hagberg B, Dahlström A. Rett syndrome: 3-D confocal microscopy of cortical pyramidal dendrites and afferents. *Neuroreport* 1994;5(12):1509-13.
 - [14] Squillaro T, Alessio N, Cipollaro M, Melone MA, Hayek G, Renieri A, et al. Reduced expression of MECP2 affects cell commitment and maintenance in neurons by triggering senescence: new perspective for Rett syndrome. *Mol Biol Cell* 2012;23(8):1435-45.
 - [15] Kishi N, Macklis JD. MECP2 is progressively expressed in post-migratory neurons and is involved in neuronal maturation rather than cell fate decisions. *Mol Cell Neurosci* 2004;27(3):306-21.
 - [16] Marchetto MC, Carroumeu C, Acab A, Yu D, Yeo GW, Mu Y, et al. A model for neural development and treatment of Rett syndrome using human induced pluripotent stem cells. *Cell* 2010;143(4):527-39.
 - [17] Harada A, Teng J, Takei Y, Oguchi K, Hirokawa N. MAP2 is required for dendrite elongation, PKA anchoring in dendrites, and proper PKA signal transduction. *J Cell Biol* 2002;158(3):541-9.
 - [18] Kaufmann WE, Naidu S, Budden S. Abnormal expression of microtubule-associated protein 2 (MAP2) in the neocortex in Rett syndrome. *Neuropediatrics* 1995;26:109-13.
 - [19] Armstrong DD. Can we relate MeCP2 deficiency to the structural and chemical abnormalities in the Rett brain? *Brain Dev* 2005;27 Suppl 1:72-76.
 - [20] McGraw CM, Samaco RC, Zoghbi HY. Adult neural function requires MeCP2. *Science* 2011;333(6039):186.
 - [21] Nguyen MV, Du F, Felice CA, Shan X, Nigam A, Mandel G, et al. MeCP2 is critical for maintaining mature neuronal networks and global brain anatomy during late stages of postnatal brain development and in the mature adult brain. *J Neurosci* 2012;32(29):10021-34.
 - [22] Kishi N, Macklis JD. MeCP2 functions largely cell-autonomously, but also non-cell-autonomously, in neuronal maturation and dendritic arborization of cortical pyramidal neurons. *Exp Neurol* 2010;222(1):51-8.
 - [23] Belichenko NP, Belichenko PV, Mobley WC. Evidence for both neuronal cell autonomous and nonautonomous effects of methyl-CpG-binding protein 2 in the cerebral cortex of female mice with Mecp2 mutation. *Neurobiol Dis* 2009;34(1):71-7.
 - [24] Ballas N, Liou DT, Grunseich C, Mandel G. Non-cell autonomous influence of MeCP2-deficient glia on neuronal dendritic morphology. *Nat Neurosci* 2009;12(3):311-7.
 - [25] Riikonen R. Neurotrophic factors in the pathogenesis of Rett syndrome. *J Child Neurol* 2003;18(10):693-7.
 - [26] Lipani JD, Bhattacharjee MB, Corey DM, Lee DA. Reduced nerve growth factor in Rett syndrome postmortem brain tissue. *J Neuropathol Exp Neurol* 2000;59(10):889-95.
 - [27] Chen WG, Chang Q, Lin Y, Meissner A, West AE, Griffith EC, et al. Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science* 2003;302(5646):885-9.
 - [28] Kaufmann WE, Johnston MV, Blue ME. MeCP2 expression and function during brain development: implications for Rett syndrome's pathogenesis and clinical evolution. *Brain Dev* 2005;27 Suppl 1:77-87.
 - [29] Vermehren-Schmaedick A, Jenkins VK, Knopp SJ, Balkowiec A, Bissonnette JM. Acute intermittent hypoxia-induced expression of brain-derived neurotrophic factor is disrupted in the brainstem of methyl-CpG-binding protein 2 null mice. *Neuroscience* 2012;206:1-6.
 - [30] Chang Q, Khare G, Dani V, Nelson S, Jaenisch R. The disease progression of Mecp2 mutant mice is affected by the level of BDNF expression. *Neuron* 2006;49(3):341-8.
 - [31] Dani VS, Chang Q, Maffei A, Turrigiano GG, Jaenisch R, Nelson SB. Reduced cortical activity due to a shift in the balance between excitation and inhibition in a mouse model of Rett syndrome. *Proc Natl Acad Sci U S A*. 2005;102(35):12560-5.
 - [32] Hamberger A, Gillberg C, Palm A, Hagberg B. Elevated CSF glutamate in Rett syndrome. *Neuropediatrics* 1992;23(4):212-3.
 - [33] Temudo T, Rios M, Prior C, Carrilho I, Santos M, Maciel P, et al. Evaluation of CSF neurotransmitters and folate in 25 patients with Rett disorder and effects of treatment. *Brain Dev* 2009;31(1):46-51.
 - [34] Samaco RC, Mandel-Brehm C, Chao HT, Ward CS, Fyffe-Maricich SL, Ren J, et al. Loss of MeCP2 in aminergic neurons causes cell-autonomous defects in neurotransmitter synthesis and specific behavioral abnormalities. *Proc*

- Natl Acad Sci U S A 2009;106(51):21966-71.
- [35] Blue ME, Naidu S, Johnston MV. Altered development of glutamate and GABA receptors in the basal ganglia of girls with Rett syndrome. *Exp Neurol* 1999;156(2):345-52.
 - [36] Lekman A, Witt-Engerström I, Holmberg B, Percy A, Svennerholm L, Hagberg B. CSF and urine biogenic amine metabolites in Rett syndrome. *Clin Genet* 1990;37(3):173-8.
 - [37] Samaco RC, Neul JL Complexities of Rett syndrome and MeCP2. *J Neurosci* 2011;31(22): 7951–7959.

1.4 Hand function and stereotypies in RTT

1.4.1 Normal hand function in infancy

The human hand is unique among primates due to its high dexterity. The relatively long thumb in combination with the mobile carpo-metacarpal saddle joint enables us to grasp and manipulated small and delicate objects. At the same time, larger objects can be grasped with force and held firmly for a long time^[1,2]. Another reason for the advanced dexterity of the human hand is the high amount of fibres in the corticospinal system, which is essential for the precision of finger skills^[3-5].

1.4.1.1 *Fine motor milestones in infancy*

Already at birth, infants can clasp small objects and keep it in their hands; yet this activity is mediated through a reflexive response and is not performed voluntarily^[7]. Infants keep their hands mainly fistled at birth but then gradually change the hand posture until the hand is preferentially open by the end of the first month. Around the age of 3 months, the grasp reflex slowly diminishes and at the same time, infants are able to grasp objects if placed in their open hand. First successful reaching of an object normally occurs during the 4th month of life and improves rapidly, resulting in a successful outcome of most reaching attempts by the end of the 5th month of life^[8-10]. Yet, the grasp component during the transition phase is still absent and the object is touched with the open hand. Furthermore, precision grasps cannot be performed at this age and grasping occurs with the whole hand (i.e. through flexion of all fingers towards the palm to enclose the object)^[9-11]. During the 4th month of life, infants start to bring their hands together in midline and reaching occurs bimanually. Grasped objects are frequently brought to the mouth in order to explore them^[8].

At 6 months, infants are able to transfer an object from one hand to the other hand, which requires the intentional release of the object by one hand. First differentiated bimanual hand activities can be seen from 9 to 10 months onwards^[8,12] The development of

independent finger movements enables the infant to perform the first precision grasps, i.e. grasping objects between the tips of the thumb and the fingers, around the 9th month of life. Later, by the end of the 11th month, small objects can be grasped with the index finger and the thumb, the so called pincer grip.^[8,13,14]

Table 1.9 describes the main milestones in fine motor development during the first year of life.

1st month	• Objects are clasped with the hands, mediated through the grasp reflex^[7,10]. • The hands are fisted most of the time^[8].
2nd month	• The child starts to explore its hands^[8]. • The hands are open most of the time^[8].
3rd month	• The grasp reflex diminishes^[8]. • Objects can be grasped voluntarily with a palmar grasp if placed in the hand^[9,10,13]. • Objects are frequently tapped^[8]. • The child is able to perceive temperature and compliance of objects^[15].
4th month	• Hand-eye coordination develops^[11]. • First reaching attempts occur^[16]. • The hands are brought together in midline^[8].
5th month	• Objects are frequently brought to the mouth (oral exploration)^[8]. • Large objects can be grabbed and lifted^[8]. • Reaching is mostly successful^[8,16].
6th month	• Objects can be transferred from one hand to the other hand^[8]. • Reaching occurs mostly bimanually^[12]. • The child becomes able to haptically perceive the texture of an object^[17].
7th month	• The infant is able to manipulate an object with one hand while stabilising it with the other hand^[18]. • Objects are often waved and banged on the table^[8].
8th month	• Handedness gradually becomes evident^[19,20]. • Grasping is successful most of the time^[12]. • Grasping with the fingers and the thumb - excluding the palm of the hand - develops^[8].
9th month	• The child gradually begins to adjust the hand shape according to the size of the object (development of the grasp component during reaching)^[21]. • First differentiated bimanual hand movements emerge. • First precision grasps might be performed^[8]. • The infant becomes able to discriminate between different weights of objects^[17,22]. • A broad repertoire of movements such as waving, banging, patting, pushing, pulling or throwing can be performed with an object^[23,24]. • Index finger pointing emerges^[8].
10th month	• Mostly unimanual reaching towards small objects^[12]. • The infant starts to develop functional play^[25,26].
11th month	• The pincer grasp emerges^[8].
12th month	• The fingers are shaped according to the object's size before they contact the object^[21]. • The infant is capable to haptically discriminate the shape of objects^[27].

Table 1.9: Milestones of fine motor development during the first 12 months of life.

1.4.1.2 Development of reaching and grasping

In adults, reaching and grasping are well coordinated and appear as a single movement. The velocity during transition rapidly increases until reaching a maximum and then gradually decelerates until the fingers come in contact with the object. During the transportation phase, opening of the hand and spreading of the fingers occur. At 60-70% of the reach, the fingers start to close and the hand shapes according to the object's size. It has been found that visual feedback is of little importance for the accurate performance of reaching and grasping and thus, the whole movement seems to be planned in advance, using visual information about the object's internal representation. The well-marked coordination of the two components suggests that the smooth performance of prehension is dependent on higher-order systems^[1,28-31].

A sufficient myelination of the optic nerve to exactly localise objects in the peri-personal space and reach them successfully does not occur before 4 to 5 months of age. Initially, the performance has an ataxic character and the infant needs several sequences of acceleration and deceleration (movement units) until reaching the object. Only by the age of 2 years, most of the children are able to perform the transition with a single movement unit. Due to their limitations of processing haptic and proprioceptive information, infants and children depend on visual input to control arm and hand movements^[1,32-34].

At birth and during early infancy, humans show a variety of reflexes, of which one is the grasp reflex. The grasp reflex, as a phylogenetically remaining behaviour, is characterised by the occurrence of a powerful grasp when the palm of the hand is stimulated. It therefore is fully developed in newborns and then gradually diminishes^[1].

Voluntary grasping usually begins at the age of 3 to 4 months. Yet, the grasp component during prehension is still absent at that time and thus, objects are touched with the open hand and subsequently grasped by a closure of the fingers towards the palm. Around 9 months of age, infants start to close their hand before they contact the object and by one year of age they are able to shape the fingers according to the object's size. The late development of the grasp component is explained by the limitations of infants to properly process visual information about the object and the inability to control distal muscles in order to perform independent finger movements^[9,11,21,35].

From around 9 to 10 months of age onwards, infants are able to perform precision grasps, which requires independent movements finger movements in order to bring the thumb to the finger tips. The development of the precision grasp is concordant with the functional

development of the corticospinal tract^[1,35,36].

1.4.1.3 Lifting an object with precision grip

The lifting of an object requires strict control of both grip force and load force. An adaptation of the grip force according to the object's properties is necessary in order to avoid damaging or dropping of the object. Objects with slippery surfaces require a higher grip force than objects with surfaces of higher friction. The load force is important to overcome the weight of the object and lift it into the desired position. The whole movement occurs in a sequence of different phases and is coordinated via the central nervous system (CNS) receiving the feedback of mechano-receptors in the palm of the hand. Studies have shown that subsequent lifts of the same object lead to invariant movement pattern, which implies a highly automatised behaviour facilitated by constant memory update^[35,37].

While in adults the grip force and the load force increase in parallel, young children apply a high grip force concomitant with negative load force to the object. Thereby they provide sufficient grip stability before the onset of the loading phase and the subsequent lift of the object. Furthermore, adults can obtain information about the object from their long-term memory, while infants depend on the constant feedback of the palmar mechano-receptors. Thus, the loading phase is characterised by "small increments, with multi-peaked force rate profiles"^[35, p111], which lead to slower execution of the lift. During the latter part of the 2nd year of life, the force rate profiles gradually adapt and by the age of 6 to 8 years, children show an almost adult-like coordination^[35,38,39].

1.4.1.4 Development of reflexive adjustments during manipulation

Appropriate fine manipulation requires mechanisms to correct unexpected changes during the process. Studies have shown that the triphasic cutaneo-muscular reflex, which is important for the adaptation of movements in response to cutaneous stimulation, only consists of a single component at birth: a spinal short-latency excitatory reflex. During the first year of life the second component - a short-latency inhibitory reflex - gradually develops. Yet, the important component for isolated finger movements - a so-called long-latency excitatory reflex routed via the cortex - appears only at 2 years of age^[35,40]. Studies have shown that the response latency when an object held with a precision grip and is suddenly loaded, is longer in 2-year-old children than in adults. Thus, infants and young

children are incapable to execute fast adaptation processes^[41,42].

1.4.1.5 Development of haptic perception

Haptic perception of certain object features is mediated via so-called exploratory procedures. These are stereotypic hand movement patterns which are automatically performed by adults during object exploration and facilitate the input of tactile information. By the application of these patterns the different properties of an object such as weight, temperature, size, compliance, texture or shape can be perceived^[43,44]. The development of haptic perception is usually concordant with the development of fine motor skills required for the different exploratory procedures. Due to the grasp reflex, small infants will clutch objects in their hands and might thus perceive the temperature, the size and to a certain extent the compliance of an object. Once differentiated finger movements can be made and objects can be grasped and manipulated, more complex patterns can be applied and the infant is capable to gain additional information about the object's properties. For example, by scratching the surface the child receives input about the texture of the object; squeezing gives information about the compliance and the object's weight can be inferred from lifting, waving or banging it^[45,46]. The exact shape of an object can usually not be explored before the infant is able to perform differentiated bimanual movements, as this advanced exploratory procedure requires both hands to act independently - one hand holds the object while the other moves the fingers around its' edges^[43,45].

Apart from the infant's motor repertoire, haptic perception is also dependent on the attention capacity of the child. Usually, humans have difficulties in processing several stimuli at the same time and this problem is even greater in infants and small children due to their immature integrational network. Different object properties hold different perceptual salience. Properties, which can be perceived during short contacts such as temperature or texture, are more salient than weight or shape. Furthermore, features which can be perceived by more than one sensory system (as for example the size of an object), often have an attentional advantage. With increasing age, children improve their capacity to process haptic information and give attention to more properties^[47].

1.4.1.6 Development of bimanual coordination and tool use

Bimanual activities can be seen early in infancy, for example when an objects is grasped

and brought to the mouth with both hands. Yet, well coordinated movements, in which each hand performs an independent, yet complementary, task, require an advanced integration of the visual and postural system as well as a high flexibility between both hands. Around the age of 7 months, infants start to manipulate an object with one hand while stabilising it with the other hand^[18]. Furthermore, they manage to complete activities in which the hands can be sequentially used. Tasks which require a differentiated but simultaneous action of both hands can normally not be performed before the age of 9 to 10 months^[12]. Fargard and Pezeacute revealed that about half of their 12- to 13-month-old study participants were able to apply differentiated strategies for the set assignment^[68]. Analysing the strategies used to retrieve an object from a closed box, Ramsay and Weber found well differentiated bimanual coordination in 78% of the 17- to 18-month-old individuals^[69].

Concerning bimanual handedness, Fargard suggested a task- and age-dependent pattern which as well might change with practice on the same task^[12]. In the study of Fagard and Pezeacute, most individuals showed no lateralisation for any of the three tasks assigned. Ramsey and Weber observed that their 17- to 19-month-old study participants showed a clear tendency to open the lid of the box with the preferred and grasp the object with the non-preferred hand^[68,69].

1.4.1.7 Development of handedness

The high amount of right-handers among humans has led many scientists to study the origin and the development of handedness. Several findings suggest a - at least partly - hereditary background, as left-handers tend to have left-handed parents and the handedness of adopted children is rather similar to their biological than to their adoptive parents^[48-52]. Some researchers suggest early signs of handedness already in utero. Hepper and colleagues found that human fetuses rather suck the right thumb than the left and preferentially move the right arm^[53,54]. Furthermore, Ververs and colleagues revealed that fetuses kept their head mainly to the right, which could further influence the tendency to right-handedness as infants predominantly use the visible hand^[55,56].

Yet, the findings about handedness in infancy have been inconsistent. Whereas older studies by Valentine and Wagner or by Giesecke revealed a greater right-hand activation for spontaneous movements in newborns^[57,58], other researchers could not find evidence for hand preference for spontaneous movements^[59,60]. Other contradictory findings concern

target-oriented movements. Ottaviano and colleagues reported a right-hand preference for target directed behaviour in 20 newborns, which was inconsistent with the results of McDonnell and colleagues, who found a greater tendency to left-hand use for movements associated with target presentation^[60,61]. Although some researcher point to a right-hand preference for early reaching^[62,63], others could not find indications for right handedness during reaching before the age of 7 to 8 months^[19,20]. In a study of 6- to 14-month-old infants, Fagard and Pezeacute revealed that most of their six study participants showed no hand preference for grasping. Yet, of the remaining, twice as many demonstrated right-handedness than left-handedness^[68]. Thus, it seems as if smaller infants show high fluctuations in hand preference and handedness is unpredictable within the first 6 months of life. Handedness for bimanual cooperation appears even later and does not become evident before the end of the first year of life^[64,65]. Hand preference gets well established between 2 and 4 years of age, with clear dominance of right-handers^[13,66,67].

1.4.1.8 Central pathways involved in hand function

Skilled hand movements are controlled by various central systems and complex pathways, which constantly interact with each other. The involved areas are distributed throughout the central nervous system (CNS). The cortical areas, which are important for general motor function are summarised as motor cortex and although the exact number of these cortical areas remains to be revealed, four regions have been found to be directly involved in hand function^[70]:

1. The primary motor cortex (M1), located in area 4
2. The secondary motor areas

The secondary motor areas further involve:

1. The premotor cortex (PM), located at the lateral part of area 6.
2. The supplementary motor area (SMA), located at the mesial part of area 6
3. The cingulate motor areas (CMA), located at the area 23 and 24

It has been supposed that M1 is the superordinated center and that the secondary motor areas can influence hand muscles only via their projections to M1^[71-73]. Yet, later studies identified direct connections from the secondary areas to the motoneurons in the spinal cord, indicating that the hand was rather controlled through a parallel than through a hierarchic system^[74-76]. The descending fibres from the motor cortex connect with the spinal motoneurons via a monosynaptic linkage. These cortico-motoneuronal projections

have been found to be important for dexterity and show a high density of fibres in humans^[3,77]. Studies on monkeys after pyramidotomy have shown, that the execution of independent finger movements relies exclusively on the corticospinal projections, whereas proximal arm muscles and power grasps are mainly controlled by subcortical circuits, involving the basal ganglia and the cerebellum^[78]. These findings were further confirmed by a study which analysed the activity of pyramidal tract neurons (CM neurons) in humans during precision and power grips. The results showed that the pyramidal tract neurons were highly active during the precision grip but not during the power grasp^[79].

Though corticospinal axons descend early to the spinal cord, the establishment of functional synapses occurs only in the second half of the first year and coincides with the development of the precision grip^[36,80]. Labelling studies of spinal grey matter in monkeys revealed that the amount of cortico-motoneuronal synapses increases with age and that dense innervation of the motoneurons to the finger muscles only occurs at 3 years of age^[81]. With advanced myelination of the descending fibres, hand and finger movements can be performed at a greater velocity^[35].

All muscles and joints involved in skilled hand function are represented in the motor cortex. It has been shown, that these representations can be altered in size, depending on the use of the linked body parts. For example, precision grip training with monkeys led to an increase of their digits' representations. If movement combinations involving various muscles and joints were used repetitively, they were joined in the same cortical representation, which suggests the establishment of specific movement patterns in the cortex^[35,82].

References for 1.4.1 Normal hand function in infancy

- [1] Koneczak J. Entwicklung der Handfunktion. In: Nowak DA, editor. *Handfunktionsstörungen in der Neurologie: Klinik und Rehabilitation*. Berlin: Springer-Verlag; 2011. p.3-10.
- [2] Napier J. The prehensile movements of the human hand. *J Bone Joint Surg* 1956;38B(4):902-13.
- [3] Bortoff GA, Strick PL. Corticospinal terminations in two new-world primates: further evidence that corticomotoneuronal connections provide part of the neural substrate for manual dexterity. *J Neurosci* 1993;13(12):5105-18.
- [4] Lawrence DG, Kuypers HG. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. *Brain* 1968;91(1):1-14.
- [5] Lemon RN. Cortical control of the primate hand. *Exp Physiol* 1993;78(3):263-301.
- [6] von Hofsten C. Predictive reaching for moving objects by human infants. *J Exp Child Psychol* 1980;30(3):369-82.
- [7] Lehmann-Horn F, Weber F. Funktionelle Neuroanatomie der Hand. In: Nowak DA, editor. *Handfunktionsstörungen in der Neurologie: Klinik und Rehabilitation*. Berlin: Springer-Verlag; 2011. p.13-22.
- [8] Touwen BCL. *Neurological development in infancy*. Cambridge: Cambridge University Press; 1976.
- [9] Halverson HM. An experimental study of prehension in infants by means of systematic cinema records. *Genet Psychol Monogr* 1931;10:107-286.
- [10] Twitchell TF. Reflex mechanisms and the development of prehension. In Connolly KJ, editor., *Mechanisms of motor skill development*. New York: Academic Press; 1970. p.25-38.

- [11] von Hofsten C, Fazel-Zandy S. Development of visually guided hand orientation in reaching. *J Exp Child Psychol* 1984;38(2):208-19.
- [12] Fagard J. Changes in grasping skills and the emergence of bimanual coordination during the first year of life. In: *The psychobiology of the hand*. Connolly KJ, editor. London: Mac Keith Press; 1998; p.123-143.
- [13] Connolly KJ, Elliott J. The evolution and ontogeny of hand function. In: *Blurton-Jones N, editor. Etiological studies of child behaviour*. Cambridge: Cambridge University Press; 1972; p.329-383.
- [14] Siddiqui A. Object size as a determinant of grasping in infancy. *J Genet Psychol* 1995;156:345-358.
- [15] Bushnell EW, Boudreau JP. Exploring and exploiting objects with the hands during infancy. In: *The psychobiology of the hand*. Connolly KJ, editor. London: Mac Keith Press; 1998; p.143-161.
- [16] von Hofsten C. Developmental changes in the organization of prereaching movements. *Dev Psychol* 1984;20:378-388.
- [17] Palmer CF. The discriminating nature of infants' exploratory actions. *Dev Psychol* 1989;25:885-893.
- [18] Kimmerle M, Mick LA, Michel GF. Bimanual role-differentiated toy play during infancy. *Infant Behav Dev* 1995;18:299-307.
- [19] Ramsay DS. Onset of unimanual handedness in infants. *Infant Behav Dev* 1980;3:377-385.
- [20] Lewkowicz DJ, Turkewitz G. Influence of hemispheric specialization in sensory processing on reaching in infants: age and gender related effects. *Dev Psychol* 1982;18:301-308.
- [21] von Hofsten C, Rönqvist L. Preparation for grasping and object: a developmental study. *J Exp Psychol [Hum Percept]* 1988;14:610-21.
- [22] Mounoud P, Bower TGR. Conservation of weight in infants. *Cognition* 1974;3:29-40.
- [23] Thelen E. Rhythmical stereotypies in normal human infants. *Anim Behav* 1979;27(Pt 3):699-715.
- [24] Ruff HA. Infants' manipulative exploration of objects: effects of age and objects characteristics. *Dev Psychol* 1984;20:9-20.
- [25] Fenson L, Kagan J, Kearsley RB, Zelazo PR. The developmental progression of manipulative play in the first two years. *Child Dev* 1976;47:232-236.
- [26] Belsky J, Most RK. From exploration to play: A cross-sectional study of infant free play behavior. *Dev Psychol* 1981;17:630-639.
- [27] Bryant PE, Jones P, Claxton V, Perkins GM. Recognition of shapes across modalities by infants. *Nature* 1972;240:303-304.
- [28] Jeannerod M. The timing of natural prehension movements. *J Motor Behav* 1984;16:235-54.
- [29] Jeannerod M. The formation of finger grip during prehension. A cortically mediated visuomotor pattern. *Behav Brain Res* 1986;19:305-19.
- [30] Wing AM, Turton A, Frase J. Grasp size and accuracy of approach in reaching. *J Motor Behav* 1986;18:245-60.
- [31] Brooks VB. Some examples of programmed limb movements. *Brain Res* 1974;71:299-308.
- [32] Brody BA, Kinney HC, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. *J Neuropathol Exp Neurol* 1987;46:283-301.
- [33] Konczak J, Dichgans J. The development toward stereotypic arm kinematics during reaching in the first 3 years of life. *Exp Brain Res* 1997;117:346-54.
- [34] Kuhtz-Buschbeck JP, Stolze H, Johnk K, Boczek-Funcke A, Illert M. Development of prehension movements in children: a kinematic study. *Exp Brain Res* 1998;122:424-32.
- [35] Forssberg H. The neurophysiology of manual skill development. In: *The psychobiology of the hand*. Connolly KJ, editor. London: Mac Keith Press; 1998; p.97-122.
- [36] Flament D, Hall EJ, Lemon RN. The development of cortico-motoneuronal projections investigated using magnetic brain stimulation in the infant macaque. *J Physiol* 1992;447:755-68.
- [37] Johansson RS, Westling G. Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp Brain Res* 1984;56(3):550-64.
- [38] Forssberg H, Eliasson AC, Kinoshita H, Johansson RS, Westling G. Development of human precision grip. I: Basic coordination of force. *Exp Brain Res* 1991;85(2):451-7.
- [39] Forssberg H, Eliasson AC, Kinoshita H, Westling G, Johansson RS. Development of human precision grip. IV. Tactile adaptation of isometric finger forces to the frictional condition. *Exp Brain Res* 1995;104(2):323-30.
- [40] Jenner JR, Stephens JA. Cutaneous reflex responses and their central nervous pathways studied in man. *J Physiol* 1982;333:405-19.
- [41] Johansson RS, Westling G. Programmed and triggered actions to rapid load changes during precision grip. *Exp Brain Res* 1988;71(1):72-86.
- [42] Eliasson AC, Forssberg H, Ikuta K, Apel I, Westling G, Johansson R. Development of human precision grip. V. anticipatory and triggered grip actions during sudden loading. *Exp Brain Res* 1995;106(3):425-33.
- [43] Lederman SJ, Klatzky RL. Hand movements: a window into haptic object recognition. *Cogn Psychol* 1987;19(3):342-68.
- [44] Klatzky RL, Lederman SJ. Toward a computational model of constraint-driven exploration and haptic object identification. *Perception* 1993;22(5):597-621.
- [45] Klatzky RL, Lederman SJ, Metzger VA. Identifying objects by touch: an "expert system". *Percept Psychophys* 1985;37(4):299-302.

- [46] Klatzky RL, Lederman SJ. Identifying objects from a haptic glance. *Percept Psychophys* 1995;57(8):1111-23.
- [47] Klatzky RL, Lederman SJ, Reed C. There's more to touch than meets the eye: the salience of object attributes for haptics with and without vision. *J Exp Psychol Gen* 1987;116:356-369.
- [48] McKeever WF. A new family handedness sample with findings consistent with X-linked transmission. *Br J Psychol* 2000;91 (Pt 1):21-39.
- [49] McManus IC. The inheritance of left-handedness. *Ciba Found Symp* 1991;162:251-81.
- [50] Risch N, Pringle G. Segregation analysis of human hand preference. *Behav Genet* 1985;15(4):385-400.
- [51] Carter-Saltzman L. Biological and sociocultural effects on handedness: comparison between biological and adoptive families. *Science* 1980;209(4462):1263-5.
- [52] Saudino K, McManus IC. Handedness, footedness, eyedness and earedness in the Colorado Adoption Project. *Br J Dev Psychol* 1998;16:167-174.
- [53] Hepper PG, Shahidullah S, White R. Handedness in the human fetus. *Neuropsychologia* 1991;29:1107-1111.
- [54] Hepper PG, McCartney GR, Shannon EA. Lateralised behaviour in first trimester human foetuses. *Neuropsychologia* 1998;36:531-534.
- [55] Ververs IA, de Vries JJ, van Geijn HP, Hopkins B. Prenatal head position from 12-38 weeks. I. Developmental aspects. *Early Hum Dev* 1994;39:83-91.
- [56] van der Meer AL, van der Weel FR, Lee DN. The functional significance of arm movements in neonates. *Science* 1995;267(5198):693-5.
- [57] Valentine WL, Wagner I. Relative arm motility in the newborn infant. *Ohio University Studies* 1934;12:53-68.
- [58] Giesecke M. The genesis of hand preference. *Monogr Soc Res Child* 1936;1(5):1-102.
- [59] Korczyn AD, Sage JJ, Karplus M. Lack of limb motor asymmetry in the neonate. *J Neurobiol* 1978;9(6):483-8.
- [60] Ottaviano S, Guidetti V, Allemand F, Spinotoli B, Seri S. Laterality of arm movement in full-term newborn. *Early Hum Dev* 1989;19(1):3-7.
- [61] McDonnell P, Anderson VES, Abraham WC. Asymmetry and orientation of arm movements in three- to eight-week-old infants. *Infant Behav Dev* 1983;6(2-3):287-98.
- [62] Coreyll JF, Michel GF. How supine postural preferences of infants can contribute toward the development of handedness. *Infant Behav Dev* 1978;1:245-257.
- [63] Michel GF. Right-handedness: a consequence of infant supine head-orientation preference? *Science* 1981;212(4495):685-7.
- [64] Michel GF, Ovrut MR, Harkins DA. Hand-use preference for reaching and object manipulation in 6- through 13-month-old infants. *Genet Soc Gen Psychol Monogr* 1985;111(4):407-27.
- [65] Ramsay DS, Campos JJ, Fenson L. Onset of bimanual handedness. *Infant Behav Dev* 1979;2:69-76.
- [66] Bates E, O'Connell B, Vaid J, Sledge P, Oakes L. Language and hand preference in early development. *Dev Neuropsychol* 1986;2:1-15.
- [67] Archer LA, Campbell D, Segalowitz SJ. A prospective study of hand preference and language development in 18- to 30-month-olds: I. Hand preference. *Dev Neuropsychol* 1988;4:85-92.
- [68] Fagard J, Pezeacute A. Age Changes in Interlimb Coupling and the Development of Bimanual Coordination. *J Mot Behav* 1997;29(3):199-208.
- [69] Ramsay DS, Weber SL. Infants' hand preference in a task involving complementary roles for the two hands. *Child Dev* 1986;57:300-307.
- [70] Roland PE, Zilles K. Functions and structures of the motor cortices in humans. *Curr Opin Neurobiol* 1996;6(6):773-81.
- [71] Roland PE, Larsen B, Lassen NA, Skinhøj E. Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J Neurophysiol* 1980;43(1):118-36.
- [72] Wise SP. The primate premotor cortex: past, present, and preparatory. *Annu Rev Neurosci* 1985;8:1-19.
- [73] Halsband U, Ito N, Tanji J, Freund HJ. The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain* 1993;116(1):243-66.
- [74] Dum RP, Strick PL. The origin of corticospinal projections from the premotor areas in the frontal lobe. *J Neurosci* 1991;11(3):667-89.
- [75] Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE. Multiple nonprimary motor areas in the human cortex. *J Neurophysiol* 1997;77(4):2164-74.
- [76] Rao SM, Binder JR, Bandettini PA, Hammeke TA, Yetkin FZ, Jesmanowicz A, et al. Functional magnetic resonance imaging of complex human movements. *Neurology* 1993;43(11):2311-8.
- [77] Phillips CG (1971) Evolution of the corticospinal tract in primates with special reference to the hand. In: Biegert J, Leutenegger W, editors. *Proceedings of the 3rd International Congress on Primatology, Zurich, 1970. Vol. 2: Neurobiology, Immunology, Cytology*. Basel. Karger, 1971. p. 2-23.
- [78] Lawrence DG, Kuypers HG. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. *Brain* 1968;91(1):1-14.
- [79] Muir RB, Lemon RN. Corticospinal neurons with a special role in precision grip. *Brain Res* 1983;261(2):312-6.
- [80] Olivier E, Edgley SA, Armand J, Lemon RN. An electrophysiological study of the postnatal development of the corticospinal system in the macaque monkey. *J Neurosci* 1997;17(1):267-76.
- [81] Armand J, Olivier E, Edgley SA, Lemon RN. Postnatal development of corticospinal projections from motor

- cortex to the cervical enlargement in the macaque monkey. *J Neurosci* 1997;17(1):251-66.
- [82] Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci* 1996;16(2):785-807.

1.4.2 The hands in RTT

1.4.2.1 Pre-regression

Girls with RTT were thought to develop normally until 6 to 18 months of age^[1]. Yet, several studies have shown that signs of abnormal behaviour and developmental deviation can be seen already in early infancy - including peculiar movements and postures of the hands^[2-9].

In a study by Burford, midwives suspected abnormalities in the infants' hand postures and movements already within the first 10 days of life. The midwives were invited to watch short video tapes of healthy infants and infants who later were diagnosed with RTT. They were blinded for the infants' clinical status and none of them had prior knowledge about RTT^[2]. Seven out of twelve infants with RTT received comments concerning their hand movements or postures, "including 'hands are very unusual', 'right hand in most unusual position', 'strange praying position of hands' and 'hand movements are strange'".^[3, p.594] (Table 1.10). Health visitors, who participated in the same study, stated their concerns about "hand posture, lack of reaching and grasping, and general hand use"^[3, p.594] in 10% of all 58 comments. Some of them observed repetitive hand-to-mouth movements among the 9- to 12-month-old infants^[3].

Infant 1 R168X	'Right hand grasp, movement of right hand. Tight grasp of left.'
Infant 2 Q244X	'Hands were turned in, been in that position for some time.'
Infant 3 R168X	'Hand movements seemed unusual, especially of right hand.'
	'Right hand has unusual claw shape.'
	'Hands very fisted, really round and tight. Right hand in most unusual position.'
	'Rotation of right hand, rotates inwards until eventually palm is open upwards to the back. At times both hands quite tightly clenched.'
Infant 4 Classic Rett, but not tested	'Hands quite firmly clenched in front. Seem to come together and clenched.'
	'Strange praying position of hands—hands so closely held together for so long is unusual.'

Table 1.10: Midwives' comments on four infants aged from birth to 10 days in a study by Burford et al[2].

Already in 1987, when the hypothesis of normal early development was still accepted by the majority of clinicians and scientists, Kerr and colleagues focussed on the research of abnormal development and behaviour before the onset of regression. They revealed excessive waving and patting of the hands as well as repetitive opening and closing of the

fingers and twisting of the wrist or arms. Furthermore the development of hand skills did not progress after the age of 10 to 12 months^[4].

Some years later, in 1990, Nomura and Segawa analysed hand stereotypies of 19 girls with RTT in order to study the pathophysiology of the disease. They found that the development of hand function was affected or delayed from mid infancy onwards. All study participants could grasp a rattle if it was placed in their hands and all except one were able to bring the hands to midline. Only eight of the 19 participants could reach out for an object and perform a pincer grasp and in all of these eight the achievement of these milestones was delayed. A transfer of object was possible in only three infants with a delay to 1 year or 1 year and 2 months of age respectively. Only three participants were able to oppose finger and thumb and the performance was clumsy and delayed^[5].

Many other researchers found abnormalities in the early development of hand function, though their studies did not focus on the hands. Repetitive hand-to-mouth movements and twisting of the hand, already described by Burford and colleagues and Kerr and colleagues, was also found in a case study by Temudo and colleagues^[2,4,6]. The girl also showed dystonic movements of the right hand and turned the hand inward during crawling. On some occasions, she kept two fingers of the left hand twisted or performed washing-like movements. Her way of object manipulation was simple and stereotyped and she systematically brought the object to the mouth^[6]. A lack of object manipulation was observed by Einspieler and colleagues in video studies of 22 girls with classic RTT during their first 6 months of life^[7]. Six of their study participants touched objects with extended fingers and did not manipulate them at 5 or 6 months of age. One girl showed excessive finger spreading during the first 2 months of life and another would keep the hand constantly fisted from 3 to 4 months of age. Repetitive opening and closing of the hand, as it had been described by Kerr, was observed in two study participants. Einspieler and colleagues further described "a small amplitude and high frequency tremor in one or both arms, independent of crying or excitement"^[7, p.698] in four infants. The first hand stereotypies could be seen from 3 months onwards, consisting of "unilateral or bilateral 1) repetitive pronation of the hand with simultaneous dorsiflexion of the wrist; 2) excessive repetitive opening and closing of both hands, sometimes even with synchronized plantar flexion of all the toes; or 3) repeated bringing of the palmar sides of both hands together (like praying), raising both hands and separating them again"^[7, p.698]

Hagberg and Witt Engerström revealed that playing behaviour was often simple;

exploratory mouthing, banging or throwing of a toy were the most advanced playing abilities^[8].

Leonard and colleagues investigated the correlation between specific mutations and deviation in the development of 320 girls with RTT during the first 10 months of life. Abnormalities in hand movements and postures were not among the main concerns of parents. Only 1.6% of them reported peculiarities in their child's hand function during the first 6 months of life. However, all of these individuals were either mutation negative or had not been tested. For the age period from 6 to 10 months, abnormalities in the development of hand function were described in 12 out of 320 (4.2%) infants. Nine individuals were mutation negative or had not been tested, whereas the remaining three had one of the seven most common mutations^[9].

Several indications for abnormalities in the development of hand function in early infancy have been found; yet, the majority of infants also display age adequate hand skills. By retrospective home video analysis of spontaneous movements in 14 individuals with RTT, Einspieler and colleagues found normal hand-to-hand and hand-to-face contact from 4 weeks onwards and one girl even showed hand-to-toe contact already at 15 weeks of age^[10]. Case studies mostly revealed that the participants learned to reach and grasp objects as well as perform pincer grasps, although with delay in some cases^[6,11,12]. In a Swedish study, more than half of the girls achieved the pincer grasp before the onset of regression^[8]. Many are able to finger feed themselves or even use a spoon or a mug^[8,11,12]. The participant with the Preserved Speech Variant in a study of Marschik and colleagues demonstrated index finger pointing to express her needs at 10 months of age^[11]. In the Swedish study, some girls were able to turn pages of a book, pick up small items or carry around an object^[8].

The results of these studies indicate that the development of hand function in infants with RTT shows constant progress until the onset of regression but that abnormalities, at the same time, are present already soon after birth.

1.4.2.2 Regression

The loss of purposeful hand function is one of the four main criteria for classic RTT. Another one is the development of hand stereotypies, which are so characteristic for this disease and led to its discovery in 1965^[13,14]. Hagberg described these two features in combination as the "single most informative and early signal of Rett Syndrome"^[15, p.726].

They are also among the main reasons to raise the concern of parents about their child's development^[15]. The median age at which hand function ceases differs between several studies. Huppke and colleagues revealed a median age of loss of hand function at 18 months; in a study by Temudo and colleagues the median age was given at 22 months and in a study by Fehr and colleagues at 27.5 months^[16-18]. About one fourth of the 849 parents interviewed in the study of Fehr and colleagues reported that their child lost hand function after the age of 36 months^[18]. However, loss of hand function usually happens before the 4th year of age. Patients who never achieved ambulation tend to show an earlier loss of fine motor skills^[16]. Furthermore, individuals with mutations associated with a more severe phenotype tend to stop using their hands at an earlier age. Fehr and colleagues revealed that RTT individuals with a p.R106W mutation showed the earliest signs of regression (defined as either loss of hand use or regression in speech) at a median age of 14.8 months. On the other hand, patients with C-terminal deletions, p.R133X or p.R294X mutations demonstrated a delayed onset of regression^[18].

A positive correlation between specific mutation types and the risk of losing hand function during the regression period has been described^[19,20]. Neul and colleagues revealed that only 8% of the 12 patients with a p.R133C mutation - associated with a milder phenotype - lost their hand function during regression, whereas in 17% it was completely preserved^[19]. Five out of 6 patients with a p.R133C mutation in a study by Temudo and colleagues were able to retain prehension; three of them even maintained feeding themselves with a spoon^[20]. In the study of Neul and colleagues, 59% of the 29 patients with a p.R168X mutation - associated with a more severe phenotype - lost their hand function completely during the regression period and 3% never acquired normal hand function. According to their results, patients with a p.R168X mutation are "one half as likely to be able to use hands"^[19, p.1318] as those with other mutations^[19]. Patients with missense or truncating mutations have shown a higher risk of hand function loss than those with deletions within the deletion hotspots. Partial or complete truncation of the NLS has been associated with an increased risk of losing normal hand function^[21]. Patients without identified mutation have been described to be less likely to lose purposeful hand function and to develop stereotypies^[22]. The degree of hand use before the onset of regression as well influences the maintenance of purposeful hand skills. Of 121 participants in a study by Larsson and colleagues, 43% could retain the ability to feed themselves with the fingers or a spoon, although some with deterioration^[23]. The age and the degree of hand function loss appear to

be a predictor for the overall severity in the long term development of patients with RTT^[15].

The pattern of how functional hand use ceases differs between the patients. Some start to show a general lack of interest in their surroundings and preferentially sit around passively. Others have been described to stop using their hands because they seem to be completely engaged by another activity. Lindberg described a girl who stopped using her hands after she had learned to walk^[24]. In a few cases, the loss of hand function occurs all of a sudden and the girls seem to be irritated and frightened by the inputs they receive through their hands^[24]. In a study by Ferr and colleagues, 23% of the 849 study participants showed a sudden loss of purposeful hand movements^[18]. Fiumara found photographic evidence of a patient, who suddenly developed typical stereotypies within 10 days after suffering from an infectious disease with high fever and a single seizure^[25]. Correlation studies about the time of hand function loss and the onset of stereotypies have led to contradictory results. While Huppke and colleagues, as well as Temudo and colleagues, found a regression of hand function before the onset of stereotypical movements in the majority of cases, Fehr and colleagues revealed that more than half of their 849 study participants showed hand stereotypies prior to hand function loss^[16,17,18]. For the remaining, Fehr and colleagues described a duration between the decrease in hand use and the development of stereotypies up to 6 months in 20%, between 6 and 15 months in about 10% and more than 15 months in another 10%^[18]. In contrast, only 18.8% of the 83 participants in the study of Temudo and colleagues demonstrated hand stereotypies before they lost their hand skills. In 43.3% loss of hand function and the onset of stereotypies coincided and the remaining patients showed a decrease in hand function before the occurrence of the first hand stereotypies^[17]. Fehr and colleagues revealed that girls with a short period between hand function loss and the onset of stereotypies are more likely to receive an early and accurate diagnosis^[18].

Stereotypies often start with circular hand-to-mouth movements, licking of the fingers and peculiar postures of the hands, which mingle with purposeful hand movements^[24,26]. In most cases the stereotypies emerge before the 4th year of life^[18]. Studies have shown that patients without a detected *MECP2* mutation develop stereotypic hand movements later than those with mutations in the gene. Furthermore, individuals with truncating mutations show first stereotypies on average 6 months earlier than those with missense mutations^[20]. Yet, unlike the age and the degree of hand skill loss, the age of onset of stereotypies is no predictor for the severity of the long term development in RTT^[15].

1.4.2.3 Post-regression

Purposeful hand function

Most girls partly or completely lose the capacity of purposeful hand use during regression and only a few are able to retrain lost skills or even acquire new abilities after the regression period^[23,27]. Larsson and colleagues analysed the self-feeding competence of 121 Swedish females with RTT. Only three individuals were able to retrain their self-feeding abilities and two learned to feed themselves after regression^[23]. In a follow-up study, Downs and colleagues found that only 4.2% of the 72 study participants were able to improve their hand skills over a period of 3 years^[27]. Patients with the Preserved Speech Variant have been reported to be more likely to retrain purposeful hand movements than those with classic RTT^[28].

Nomura and Segawa reported that hand function in individuals with RTT is mostly limited to gross hand manipulation^[5]. Yet, many researchers have found a wide range of capacity in hand use among their study participants. Although one third of the 144 patients in a study by Downs and colleagues had no functional hand use at all, about 40% were able to manipulate small objects and 13% could even transfer objects from one hand to the other. Small object manipulation was seen especially during finger feeding^[29]. Lindberg reported that all of her 39 study participants could reach out and touch an object and about half of them were able to grasp it, although they performed this movement only occasionally^[24]. Umansky and colleagues revealed that patients with RTT were less able to execute externally directed hand movements such as prehension, object manipulation or self-feeding than to perform movements directed to their own bodies, for example rubbing the eyes. The parents of two thirds of the 145 study participants reported that their child never used a spoon or a fork and about half of the individuals were unable to hold a bottle or a cup or to finger feed. The most frequently performed external task was touching of an object. About 90% of the participants were able to rub their eyes and almost 82% could scratch themselves^[30]. The extent and levels of functional hand use also vary among the different types of mutation. As to expect, the highest percentages of individuals with functional hand use have been found among those with mutations associated with milder phenotypes^[19]. Furthermore, these patients also showed the highest levels of hand function with the majority being able to manipulate small objects even with scissor or pincer grasp^[29]. By contrast, individuals with mutations associated with a higher overall severity, tend to have the poorest hand use (Figure 1.10)^[19]. Neul and colleagues described that only

38% of the 29 study participants with a p.R168X mutation were able to use their hands^[19]. The average of the patients with the same mutation in a study of Downs and colleagues were unable to hold a large object for at least 2 seconds.

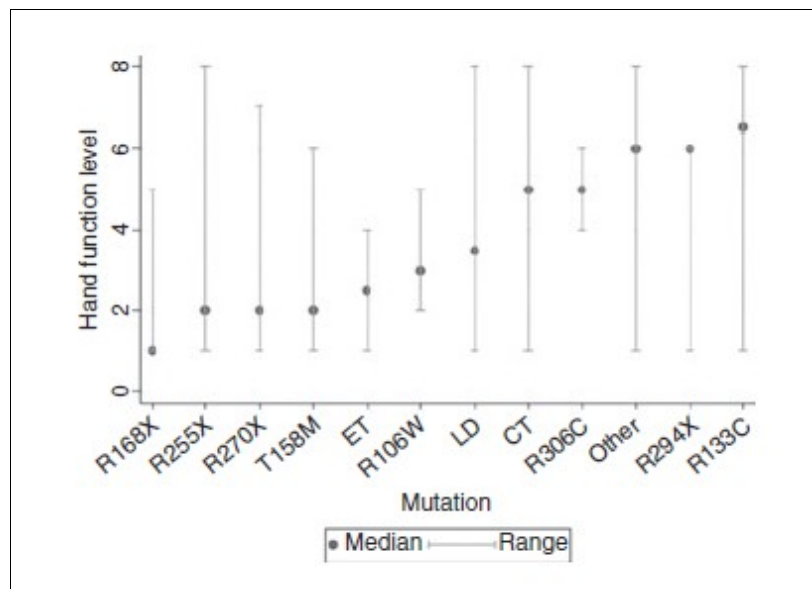


Figure 1.10: Level of purposeful hand function associated with each of the common mutations in 144 participants of a study by Downs and colleagues^[29]. ET=early truncating mutation, LD=large deletions, CT=C-terminal mutations.

Downs and colleagues also revealed lower hand skill levels in non-ambulant patients and in those older than 19 years^[29]. The latter confirms the common finding that the capacity to carry out purposeful hand movements decreases with age, when rigidity and hypokinesia become prominent^[24]. Yet, ageing affects hand function to a lesser extent than gross motor function^[27,31]. In their follow-up study, Downs and colleagues showed that about 40% of the participants lost hand skills to a certain degree whereas almost 60% were able to retain their abilities and a small number could even improve their hand function. They further revealed that patients with highest or lowest degrees of hand use at baseline were more likely to lose abilities, which was also true for individuals who were unable to finger feed or to walk at baseline. Between the different age groups, the highest percentage of those who maintained abilities was among the adolescents whereas patients younger than 8 years or older than 19 years showed a greater tendency of losing skills^[27].

The main reason for the impaired hand function in patients with RTT is most probably a malfunction of both motor and sensory systems in the CNS. The resulting dyspraxia hinders the individuals to initiate and perform movements correctly, although their desire

to use their hands doesn't seem to be disrupted^[26,32]. In her book, Lindberg described a girl who, before regression, always took her toys out of a shelf. After the regression period, she was often watched standing in front of the same shelf, staring at the toys and showing clear signs of distress such as hyperventilation, teeth grinding, intense stereotypic hand movements and a tense body posture^[32]. Even if the individuals are able to reach out for an object, they are often unable to grab it and instead hit the object or, if they achieve to grasp it, they are incapable to keep it in their hands. Lindberg suggested that movements which are consciously controlled are more difficult to be performed than if they "originate[s] spontaneously from their feelings in a particular situation or for an object."^[24, p.39] She mentioned that girls could suddenly grasp and manipulate an object and even do this in a smooth and well coordinated manner. Yet, this situations occur only rarely and maybe just once in a lifetime^[24].

Hand preference

Several studies have shown that there is a lower prevalence of right-handedness among individuals with cognitive impairment compared to the normal population, in which about 90% are right-handed^[33-35]. Regarding RTT, similar findings have been described by various researchers. Olson and Rett suggested a delay in the establishment of right-handedness, as most of their study participants shifted from left- to right-hand preference around the age of 7 years^[36]. However, these results could not be confirmed by other studies. Umansky and colleagues even refuted this assertion by analysing hand preference for both simple and complex tasks in individuals with RTT. They revealed a greater extent of laterality for complex than for simple tasks which is incompatible with the idea of a late establishment of handedness^[30].

Though the numbers vary between the different studies, the majority of researchers found an equal distribution of right-handers, left-handers and individuals without hand preference among their study participants (Figure 1.11)^[23,26,36]. Most of them admitted the difficulty in analysing handedness in RTT due to severe cognitive impairment and the restriction in purposeful hand use in the individuals. Yet, studies of hand preference in patients with the Preserved Speech Variant, who often show better hand function, have revealed a similar distribution of handedness to that found among individuals with classic RTT^[26].

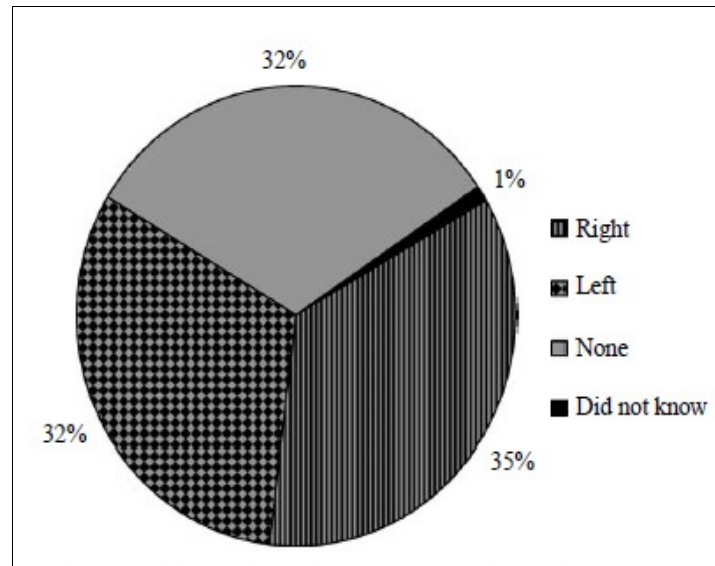


Figure 1.11: Distribution of preferred hand in 88 participants of a retrospective parental questionnaire study by Larsson et al[23].

Interestingly, comparing hand preference for functional hand use with the laterality of stereotypic hand behaviour, Carter and colleagues found that the hand which was predominantly affected by stereotypies was - in many individuals - also preferentially used to carry out purposeful movements^[37]. Marschik and colleagues observed the opposite in a girl with the Preserved Speech Variant, who preferentially used her left hand while stereotypies were predominantly seen in the right hand^[11].

Hand stereotypies

Hand stereotypies are a characteristic symptom of RTT and affect the vast majority of patients with a prevalence of about 95%^[18,37]. After their onset during the regression period they are present throughout life, although changes in intensity and amplitude have been found^[39,41]. Usually, the individuals perform repetitive, rhythmic and mostly simple movements with their hands either together or separated^[4,17]. A specific pattern for the hand stereotypies in RTT has not been found and each female displays her own, individual movement sequences (Figure 1.13). Furthermore, each hand moves independently from its partner, which can be seen especially when the hands are apart. One hand might be pulling the hair while the other is put into the mouth (Figure 1.13 H)^[4,38,39]. Motion analysis of hand stereotypies in a 3-year-old girl with RTT has shown that even when the hands are together the frequency and amplitude of the movements of each hand are similar but not equal^[40].

A common finding is that patients with RTT hardly ever look at their hands while performing the stereotypic movements, which is different to individuals with autism or cognitive impairment^[4,38]. Temudo and colleagues found this feature especially among mutation-positive study participants. None of the females in their study watched her hands while performing these odd movements^[17]. The stereotypies disappear completely when the patients are asleep but are often continuously present during waking hours^[17,43,42]. In a study by Carter and colleagues, about 90% of the parents of 144 individuals with RTT described constant or frequent hand stereotypies in their child. Only 3% reported that stereotypic movements of the hands were rare or absent^[37]. Temudo and colleagues found constant hand stereotypies in about 60% of their 60 study participants^[41]. Carter and colleagues further investigated the correlation between the frequency of hand stereotypies and specific mutation types. About half of the patients with p.R294X or C-terminal mutations had constant hand stereotypies, in contrast to those with mutations associated with a more severe phenotype which showed a lower frequency of stereotypic hand behaviour. The authors suggested that the higher overall restriction of movements in more severely affected patients would also restrain the stereotypic movements^[37].

With increasing age, when rigidity and hypokinesia become more prominent, stereotypies occur less frequently and become slower and simpler, although the type of movements is commonly maintained^[17]. They also get less intense and the hands are often kept together firmly, difficult to be separated. Only those adults, who maintain good ambulation skills and psychomotor activities have been described to retain intense and complex patterns of stereotypies^[39].

A common finding is that the emotional state of the patient influences the intensity of the stereotypies. Parents have reported that the stereotypic hand behaviours diminish when their child is ill or her attention is drawn by input around her^[39,44]. In contrast, agitation, both positive and negative, often leads to an increase in intensity^[4,39]. Most patients are unable to stop these involuntary movements even though they are clearly interested in reaching out or grasping something, for example food. As a consequence they often become irritated and stereotypies increase in intensity^[4,39]. Elian and Rudolf and colleagues found an interrelationship between hand stereotypies and breathing abnormalities in 72% of their 25 study participants, though it did not follow a specific pattern. In some, hand stereotypies increased in parallel with hyperventilation while in others the correlation was inverse; stereotypic hand movements ceased during hyperventilation or breathing became

normal when stereotypies increased^[44].

Environmental conditions seem to have little or no influence on the frequency of the stereotypic behaviour. Wales and colleagues studied hand stereotypies in 8 adolescent females during four different set conditions. The participants were either: 1) alone in the room, 2) alone with their favoured music playing, 3) together with an adult who interacted with them or 4) together with an adult who placed different toys in their hands. Hand stereotypies were present in all females and, in the majority, occurred almost continuously. Six of the 8 participants showed no change in the frequency of stereotypies during any of the settings and the remaining two only responded in two situations. In one, stereotypies decreased when she was alone with her favourite music playing. The other showed an increase of hand stereotypies when she was completely alone in the room^[45].

The majority of individuals with RTT display more than one hand stereotypy. Including involuntary movements of other body part, Temudo and colleagues revealed that about one third of the 83 study participants showed five or more different stereotypic movements^[17]. Carter and colleagues described a median number of 2 and a maximum number of 6 different hand stereotypies per patient. In total, they identified 15 different stereotypy patterns among their 144 patients. More than half of those younger than 8 years performed more than two stereotypies, compared to only one third of those older than 19. Thus, in addition to the decrease in frequency and intensity of stereotypic behaviour, also the number of different patterns decreases when the patients get older^[37]. Temudo and colleagues found an association between the number of hand stereotypies and p.R294X and p.T158M mutations, as patients with one of these two mutations showed an increased variability of stereotypic movements^[20].

The most common hand stereotypies are wringing and washing movements of the hands with an occurrence in about 60-75%. This pattern is often associated with a simultaneous mouthing of both hands. Mouthing of one hand is the most common hands-apart stereotypy and affects about 36-40% of the patients. Other frequent stereotypic movements are clapping of one hand, clapping, hair pulling, tapping or hand gaze^[17,37]. Some of these stereotypies have been revealed to be associated with specific mutations. The highest percentages of hand clapping have been found among patients with p.R306C and early truncating mutations, whereas the same patients tend to display less hand wringing stereotypies. Single handed mouthing is more common in individuals with p.R306C and C-terminal mutations, whereas bilateral mouthing is more frequently seen in patients with

p.T158M mutations^[37]. In a study by Temudo and colleagues, all 9 participants with a p.R168X mutation had permanent hands-apart stereotypies^[20]. The age of the patients also seems to influence the type of stereotypies, as clapping, mouthing, tapping and clasping are less prevalent in older patients and hand wringing is seen more often^[37]. The latter is contradictory to the reports that patients maintain the same stereotypy patterns throughout life^[41].

Temudo and colleagues found that about 20% of their 83 study participants showed stereotypies with joined hands only and another 20% had only hands-apart stereotypies. The remaining patients displayed both stereotypies with joined and with separated hands^[17]. Elian and Rudolf described that 44% of the 25 individuals in their study had hands-apart stereotypies and about 20% demonstrated stereotypic hand behaviour only in one hand and, interestingly, they used the same hand to perform purposeful hand movements^[44]. This finding, together with the results of Carter and colleagues^[37] (see above), indicate that hand stereotypies do not prevent purposeful hand use.

1.4.2.4 Pathophysiology of hand function loss and stereotypies

The time of hand function loss together with the results of neuropathological studies have led to some suggestions about the pathophysiological process underlying the deterioration of hand use in patients with RTT. The decrease of purposeful hand movements usually occurs in mid-infancy, a time when healthy infants rapidly improve their abilities for object-orientated hand use^[46,47]. The latter requires the establishment of a neural network through synapse formation and rearrangement, dendritic-axonal growth, controlled cell proliferation and apoptosis^[48]. Neuroimaging studies in patients with RTT have shown a reduction in size and dendritic arborisation in some regions of the brain, including the dorsal parietal lobe^[49,50]. The dorsal parietal lobe has been found to play an essential role in integrating sensory input and generating arm and hand movements^[51]. Thus, deficits in the neuronal connectivity of this brain region most probably lead to a disruption of the complex circuitry required for purposeful hand use and cause the loss of hand function in RTT.

Regarding hand stereotypies, different hypotheses of the pathophysiological mechanism have been constructed. Stereotypical hand movements are physiological in infants and are driven by subcortical rhythm generators. With the maturation of the cortical network, these stereotypies are more and more repressed and converted into purposeful hand

movements^[52,53]. Kerr suggested that the cortical abnormalities in RTT lead to a failure in the inhibition of the subcortical generators, which in turn induce repetitive and rhythmic movements^[54]. A neuroimaging study of healthy males with complex hand stereotypies revealed a decrease in frontal white matter and a reduction of the volume of the caudate nuclei, indicating a dysfunction of cortico-striatal-thalamo-cortical pathways as basis for the development of stereotypies^[55]. It has further been suggested that a defect in the dopaminergic system in the basal ganglia may also contribute to the presence of stereotypical behaviours. Intra-striatal and systemic pre- and postsynaptic injection of dopamine or active dopamine agonists led to a number of stereotypic movements in rats. While D2 agonists induced stereotypic behaviour, D1 agonists only enhanced the stereotypies^[56,57]. In some autistic children, elevated levels of β -endorphins have been found in the plasma and the cerebrospinal fluid and treatment with opiate blockers improved their self-injurious, stereotypic movements^[58].

Though some hypotheses have been constructed, the pathophysiology of both hand function loss and the development of stereotypies is not fully understood and further investigations are necessary to reveal the underlying mechanisms.

References for 1.4.2 The hands in RTT

- [1] Trevathan E, chairperson. Diagnostic criteria for Rett syndrome. The Rett Syndrome Diagnostic Criteria Work Group. *Ann Neurol* 1988;23(4):425-8.
- [2] Burford B. Perturbations in the development of infants with Rett disorder and the implications for early diagnosis. *Brain Dev* 2005;27 Suppl 1:3-7.
- [3] Burford B, Kerr AM, Macleod HA. Nurse recognition of early deviation in development in home videos of infants with Rett disorder. *J Intellect Disabil Res* 2003;47(8):588-96.
- [4] Kerr AM, Montague J, Stephenson JB. The hands, and the mind, pre- and post-regression, in Rett syndrome. *Brain Dev* ;9(5):487-90.
- [5] Nomura Y, Segawa M. Characteristics of motor disturbances of the Rett syndrome. *Brain Dev* ;12(1):27-30.
- [6] Temudo T, Maciel P, Sequeiros J. Abnormal movements in Rett syndrome are present before the regression period: a case study. *Mov Disord* 2007;22(15):2284-7.
- [7] Einspieler C, Kerr AM, Prechtl HF. Is the early development of girls with Rett disorder really normal?. *Pediatr Res* 2005;57(5):696-700.
- [8] Hagberg B, Witt Engerström I. The Swedish series of females with Rett syndrome 1960-92. In: Hagberg B, editor. *Rett syndrome - clinical and biological aspects*. London: Mac Keith Press; 1993. p.21-26.
- [9] Leonard H, Moore H, Carey M, Fyfe S, Hall S, Robertson L, et.al. Genotype and early development in Rett syndrome: The value of international data. *Brain Dev* 2005;27 Suppl 1:59-68.
- [10] Einspieler C, Kerr AM, Prechtl HF. Abnormal general movements in girls with Rett disorder: the first four months of life. *Brain Dev* 2005;27 Suppl 1:8-13.
- [11] Marschik PB, Einspieler C, Oberle A, Laccone F, Prechtl HF. Case report: Retracing atypical development: a preserved speech variant of Rett syndrome. *J Autism Dev Disord* 2009;39(6):958-61.
- [12] Hagberg B.J. Rett syndrome: long-term clinical follow-up experiences over four decades. *Child Neurol* 2005;20(9):722-7.
- [13] Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al for the RettSearch Consortium. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* 2010;68(6):944-50.
- [14] International Rett Syndrome Foundation. About Rett Syndrome - History. <http://www.rett Syndrome.org/content/blogcategory/13/969>; accessed March 25th, 2012.
- [15] Hagberg B.J. Rett syndrome: long-term clinical follow-up experiences over four decades. *Child Neurol* 2005;20(9):722-7.
- [16] Huppke P, Held M, Laccone F, Hanefeld F. The spectrum of phenotypes in females with Rett syndrome. *Brain*

- Dev 2003;25:346-51.
- [17] Temudo T, Oliveira P, Santos M, Dias K, Vieira J, Moreira A, et al. Stereotypies in Rett syndrome: analysis of 83 patients with and without detected MECP2 mutations. *Neurology* 2007;68(15):1183-7.
 - [18] Fehr S, Downs J, Bebbington A, Leonard H. Atypical presentations and specific genotypes are associated with a delay in diagnosis in females with Rett syndrome. *Am J Med Genet A* 2010;152A(10):2535-42.
 - [19] Neul JL, Fang P, Barrish J, Lane J, Caeg EB, Smith EO, et al. Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. *Neurology* 2008;70(16):1313-21.
 - [20] Temudo T, Santos M, Ramos E, Dias K, Vieira JP, Moreira A, et al. Rett syndrome with and without detected MECP2 mutations: an attempt to redefine phenotypes. *Brain Dev* 2011;33(1):69-76.
 - [21] Huppke P, Held M, Hanefeld F, Engel W, Laccone F. Influence of mutation type and location on phenotype in 123 patients with Rett syndrome. *Neuropediatrics* 2002;33(2):63-8.
 - [22] Lima FT, Brunoni D, Schwartzman JS, Pozzi MC, Kok F, Juliano Y, et al. Genotype-phenotype correlation in Brazilian Rett syndrome patients. *Arq Neuropsiquiatr* 2009;67(3A):577-84.
 - [23] Larsson G, Lindström B, Engerström IW. Rett syndrome from a family perspective: The Swedish Rett Center survey. *Brain Dev* 2005;27 Suppl 1:14-19.
 - [24] Lindberg B. Understanding Rett syndrome: a practical guide for parents, teachers, and therapists. Cambridge,MA: Hogrede & Huber Publishers; 2006. p.37-44.
 - [25] Fiumara A, Barone R, D'Asero G, Marzullo E, Pavone L. Rett syndrome: photographic evidence of rapid regression. *J Child Neurol* 1999;14(8):550-2.
 - [26] Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.1-26.
 - [27] Downs J, Bebbington A, Kaufmann WE, Leonard H. Longitudinal hand function in Rett syndrome. *J Child Neurol*. 2011;26(3):334-40.
 - [28] Zappella M. The preserved speech variant of the Rett complex: a report of 8 cases. *Eur Child Adolesc Psychiatry* 1997;6 Suppl 1:23-5.
 - [29] Downs J, Bebbington A, Jacoby P, Williams AM, Ghosh S, Kaufmann WE, et al. Level of purposeful hand function as a marker of clinical severity in Rett syndrome. *Dev Med Child Neurol* 2010;52(9):817-23.
 - [30] Umansky R, Watson JS, Colvin L, Fyfe S, Leonard S, de Klerk N, et al. Hand preference, extent of laterality, and functional hand use in Rett syndrome. *J Child Neurol* 2003;18(7):481-7.
 - [31] Foley KR, Downs J, Bebbington A, Jacoby P, Girdler S, Kaufmann WE, et al. Change in gross motor abilities of girls and women with rett syndrome over a 3- to 4-year period. *J Child Neurol* 2011;26(10):1237-45.
 - [32] Lindberg B. Understanding Rett syndrome: a practical guide for parents, teachers, and therapists. Cambridge,MA: Hogrede & Huber Publishers; 2006. p.35-37.
 - [33] Mandal MK, Pandey G, Das CT, Bryden MP. Handedness in mental retardation. *Laterality* 1998;3(3):221-5
 - [34] Leconte P, Fagard J. Lateral preferences in children with intellectual deficiency of idiopathic origin. *Dev Psychobiol* 2006;48(6):492-500
 - [35] Coren S, Porac C. Fifty centuries of right-handedness: the historical record. *Science* 1977;198(4317):631-2.
 - [36] Olsson B, Rett A. Shift to righthandedness in Rett syndrome around age 7. *Am J Med Genet Suppl* 1986;1:133-41.
 - [37] Carter P, Downs J, Bebbington A, Williams S, Jacoby P, Kaufmann WE, et al. Stereotypical hand movements in 144 subjects with Rett syndrome from the population-based Australian database. *Mov Disord*. 2010 Feb 15;25(3):282-8.
 - [38] Temudo T. Movement disorder in Rett syndrome. In: Nardocci N, Fernandez-Alvarez E, editors. *Movement disorders in children: a clinical update with video recordings*. Montrouge: John Libbey Eurotext; 2007. p.153-167.
 - [39] Lindberg B. Understanding Rett syndrome: a practical guide for parents, teachers, and therapists. Cambridge,MA: Hogrede & Huber Publishers; 2006. p.32-35.
 - [40] Wright M, Van der Linden ML, Kerr AM, Burford B, Arrowsmith G, Middleton RL. Motion analysis of stereotyped hand movements in Rett syndrome. *J Intellect Disabil Res* 2003;47(Pt 2):85-9.
 - [41] Temudo T, Ramos E, Dias K, Barbot C, Vieira JP, Moreira A, et al. Movement disorders in Rett syndrome: an analysis of 60 patients with detected MECP2 mutation and correlation with mutation type. *Mov Disord* 2008;23(10):1384-90.
 - [42] Lotan M, Shapiro M. Management of young children with Rett disorder in the controlled multi-sensory (Snoezelen) environment. *Brain Dev* 2005;27 Suppl 1:88-94.
 - [43] Percy AK, Lane JB. Rett syndrome: model of neurodevelopmental disorders. *J Child Neurol* 2005;20(9):718-21.
 - [44] Elian M, de M Rudolf N. Observations on hand movements in Rett syndrome: a pilot study. *Acta Neurol Scand* 1996;94(3):212-4.
 - [45] Wales L, Charman T, Mount RH. An analogue assessment of repetitive hand behaviours in girls and young women with Rett syndrome. *J Intellect Disabil Res* 2004;48(Pt 7):672-8.
 - [46] Umansky R, Watson JS, Hoffbuhr K, Painter KM, Devaney J, Hoffman E. Social facilitation of object-oriented hand use in a Rett syndrome variant girl: implications for partial preservation of an hypothesized specialized cerebral network. *J Dev Behav Pediatr* 2001;22(2):119-22.

- [47] White B, Castle P, Held R. Observations on the development of visually-directed reaching. *Child Dev* 1964;35:349-364.
- [48] Volpe JJ. Overview: normal and abnormal human brain development. *Ment Retard Dev Disabil Res Rev* 2000;6(1):1-5
- [49] Armstrong DD. Neuropathology of Rett syndrome. *J Child Neurol* 2005;20(9):747-53.
- [50] Carter JC, Lanham DC, Pham D, Bibat G, Naidu S, Kaufmann WE. Selective cerebral volume reduction in Rett syndrome: a multiple-approach MR imaging study. *AJNR Am J Neuroradiol*. 2008 Mar;29(3):436-41
- [51] Fogassi L, Luppino G. Motor functions of the parietal lobe. *Curr Opin Neurobiol* 2005;15:626-631.
- [52] Thelen E. Rhythmical stereotypies in normal human infants. *Anim Behav* 1979;27(Pt 3):699-715.
- [53] Thelen E. Rhythmical behaviour in infancy: an ethological perspective. *Dev Psychol* 1981;17:237-257.
- [54] Kerr AM. Early clinical signs in the Rett disorder. *Neuropediatrics* 1995;26(2):67-71.
- [55] Kates WR, Lanham DC, Singer HS. Frontal white matter reductions in healthy males with complex stereotypies. *Pediatr Neurol* 2005;32(2):109-12.
- [56] Costall B, Naylor RJ, Cannon JG, Lee T. Differentiation of the dopamine mechanisms mediating stereotyped behaviour and hyperactivity in the nucleus accumbens and caudate-putamen. *J Pharm Pharmacol* 1977;29(6):337-42
- [57] Koller WC, Herberster G. D1 and D2 dopamine receptor mechanisms in dopaminergic behaviors. *Clin Neuropharmacol* 1988;11(3):221-31.
- [58] Sandman CA. Beta-endorphin dysregulation in autistic and self-injurious behavior: a neurodevelopmental hypothesis. *Synapse* 1988;2(3):193-9.

1.4.3 Therapeutic options

Most patients with RTT are unable to carry out purposeful hand movements, although they often clearly want to reach or grasp an object. Hanks commented that it is "evident that the girls would like to do something else with their hands but cannot break through the hand wringing to do so"^[1, p.250]. Researchers are still in disagreement whether hand stereotypies impede purposeful hand use and thus, hand function could be improved by the restriction of these stereotypies. Especially in the late eighties and early nineties, the effects of hand splints and elbow orthoses on the extent of hand stereotypies and functional hand use were studied by several scientists^[2-6]. Yet, the results were contradictory. Naganuma and Billingsley^[2] analysed the ramification of hand splints in three adolescent girls with RTT during free time and during feeding sessions. They found a clear decrease in the extent of hand stereotypies in all three girls as soon as the splints were applied. Furthermore, one participant, who was able to finger feed at baseline, improved her skills and finished her meal in a shorter time. After removal of the splints, stereotypical movements increased again in all participants and in two, the mean level after withdrawal even exceeded the baseline level^[2]. In a case study of a 20-year-old woman with RTT, Kubas^[3] showed an improvement of hand function through the application of a dorsal wrist splint together with splints on the thumb and the index finger. After almost four years of therapy, the patient, who was unable to grasp or release an object at baseline, could often bring a spoon to her mouth and put it back on the plate. Furthermore, she was occasionally able to open her thumb and her index finger and place it on the food^[3].

Though these two studies showed clear evidence of the positive effects of hand splints on functional hand use and the restriction of hand stereotypies, other researchers could not validate these findings. Using the same type of splints as Naganuma and Billingsley^[2], Tuten and Miedaner^[4] found neither a decrease of stereotypic movements nor an increase of purposeful hand use during the intervention sessions in two 5-year-old girls with RTT. Furthermore - different to the original study - their participants did not exceed the baseline levels of stereotypic hand movements after withdrawal of the splints^[4]. Sharpe^[5] as well found no evidence for an improvement of hand function or the restriction of stereotypies through hand splints in two 6-year-old girls with RTT. Yet, she revealed that both girls showed an increase in hand-to-toy contact and that their stereotypic behaviours diminished when they were wearing an elbow orthosis. In one participant, the extent of hand-to-toy contact was even higher than that of stereotypies when the elbow was restrained by the orthosis^[5]. In a case study, Sharpe and Ottenbacher, could confirm that the application of an elbow orthosis led to a decrease in hand stereotypies, yet the improvement of finger-feeding skills in their participant was minimal^[6].

However, the inconsistency of these studies' results is not the only reason why the use of splints and orthoses is often critically judged. Some researchers and parents reported that the stereotypic behaviour would have a meaning for the child and that it was a way of expression. Many girls are able to communicate their feelings through the intensity of their stereotypies^[7-10]. Patients might also get irritated by the unfamiliar sensory input they get through the restraints and respond with agitation or fear^[11,12]. Although she did not observe any of these features in her study participant, Sharpe still admitted that the "use of the elbow orthosis include[s] the possibility of frustration and discomfort for the wearer due to being restrained"^[5, p.138] and that "the wearer might exhibit an increase in the intensity of stereotypic hand movements immediately after the orthosis is removed."^[5, p.139]. Sharpe and Ottenbacher stated that "a child who demonstrates more skilled bilateral hand use or who has not developed a strong hand preference might be frustrated by a restraint and might possibly benefit more from splinting"^[6, p.332].

In recent years, intervention with restrictive methods has become less prominent and focus has been set on reinforcement of voluntary movements through sensory stimulation. Though Wales and colleagues found no clear evidence that environmental manipulation influences the extent of stereotypic behaviour^[13], Iwata and colleagues were able to decrease the hand-biting behaviour in two girls with RTT and they even increased the time

of toy-play in one participant by using differential reinforcement in combination with response-interruption^[14]. A study by Kondo and colleagues revealed that environmental enrichment could ameliorate motor coordination and reduce stereotypic movements in *Mecp2* mutant mice^[15]. Lotan and Shapiro^[16] found an improvement of a variety of symptoms in their patients during and after several interventions in a Snoezelen environment. According to them, thick mattresses led to a better proprioceptive stimulation to the hands and thus, facilitated functional hand use. Additionally, many patients showed a decrease of hand stereotypies after they had touched vibrating materials^[16]. Hydrotherapy is an option for those who like to be in the water. In a case study of an 11-year-old girl with classic RTT, Bumin and colleagues found that stereotypies continuously decreased and hand skills improved during a 8-week-period in which hydrotherapy was applied twice a week^[17].

An important factor for an efficient therapy is the motivation of the patients. Some girls get frustrated by their inability to carry out purposeful movements and subsequently give up trying. Thus, it is necessary to keep the demands low and find objects and tasks which raise the patients interest^[10]. Lotan and Shapiro suggested that the variety of visual stimuli in a Snoezelen environment are suitable to keep the patients' attention and encourage them to use their hands^[16]. As individuals with RTT have often been described to be very fond of music, some researchers have investigated the effect of music therapy on functional hand use in RTT^[18-20]. Yasuhara and Sugiyama revealed that, after several sessions of music therapy, the study participants showed an increase in the frequency of grasping and could keep objects in their hands for a longer time^[18]. In a case report, Wigram and Lawrence^[19] described a 6-year-old girl who displayed good response to instrumental music. Her stereotypic movements diminished and she was able to hit the piano keys and strum the strings of a guitar. Furthermore, she used both hands to hit a large drum and even managed to beat it with a short handled beater. In addition to the improvement of hand function, the patient produced vocal sounds and maintained good eye contact during the session^[19]. Go and Mitani^[20] discovered that stereotypic body movements could help patients to carry out purposeful hand movements. By playing a simple regular rhythm they induced repetitive back-and-forth body movements in some of their study participants. Together with the body stereotypies, the patients began to perform rhythmical movements with their hands and, subsequently, were able to hit a tambourine which was placed in front of them^[20].

Independent of which kind of treatment is chosen, one needs to keep in mind, that patients

with RTT might easily overreact to unfamiliar situations. Thus, a well established relationship with the therapist and precaution in the implementation of new material is necessary. Furthermore the therapy needs to be planned according to the patients' possibilities and needs^[11]. Entering the regression period, some girls seem to get afraid of their hands and for them, it is not suitable to focus on their fine manipulation skills. Instead they should be encouraged to regain a positive affiliation to their hands^[10]. Others might require the application of restrictive therapy such as splints or orthoses as their repetitive hand-to-mouth movements would otherwise lead to severe tissue damage on the hands^[2,14].

References for 1.4.3 Therapeutic options

- [1] Hanks SB. The role of therapy in Rett syndrome. *Am J Med Genet Suppl* 1986;1:247-52.
- [2] Naganuma GM, Billingsley FF. Effect of hand splints on stereotypic hand behavior of three girls with Rett syndrome. *Phys Ther* 1988;68(5):664-71.
- [3] Kubas ES. Use of splints to develop hand skills in a woman with Rett syndrome. *Am J Occup Ther* 1992;46(4):364-8.
- [4] Tuten H, Miedaner J. Effect of hand splints on stereotypic hand behavior of girls with Rett syndrome: a replication study. *Phys Ther* 1989;69(12):1099-103.
- [5] Sharpe PA Comparative effects of bilateral hand splints and an elbow orthosis on stereotypic hand movements and toy play in two children with Rett syndrome. *Am J Occup Ther* 1992;46(2):134-40.
- [6] Sharpe PA, Ottenbacher KJ. Use of an elbow restraint to improve finger-feeding skills in a child with Rett syndrome. *Am J Occup Ther* 1990;44(4):328-32.
- [7] Lindberg B. Understanding Rett syndrome: a practical guide for parents, teachers, and therapists. Cambridge,MA: Hogrefe & Huber Publishers; 2006. p.32-35.
- [8] Elian M, de M Rudolf N. Observations on hand movements in Rett syndrome: a pilot study. *Acta Neurol Scand* 1996;94(3):212-4.
- [9] Kerr AM, Montague J, Stephenson JB. The hands, and the mind, pre- and post-regression, in Rett syndrome. *Brain Dev* ;9(5):487-90.
- [10] Lindberg B. Understanding Rett syndrome: a practical guide for parents, teachers, and therapists. Cambridge,MA: Hogrefe & Huber Publishers; 2006. p.98-118.
- [11] Lotan M, Hanks S. Physical therapy intervention for individuals with Rett syndrome. *Scientific World Journal* 2006 10;6:1314-38.
- [12] Mount RH, Hastings RP, Reilly S, Cass H, Charman T. Behavioural and emotional features in Rett syndrome.
- [13] *Disabil Rehabil* 2001;23(3-4):129-38. Review.
- [14] Wales L, Charman T, Mount RH. An analogue assessment of repetitive hand behaviours in girls and young women with Rett syndrome. *J Intellect Disabil Res* 2004;48(Pt 7):672-8.
- [15] Iwata BA, Pace GM, Willis KD, Gamache TB, Hyman SL. Operant studies of self-injurious hand biting in the Rett syndrome. *Am J Med Genet Suppl* 1986;1:157-66.
- [16] Kondo M, Gray LJ, Pelka GJ, Christodoulou J, Tam PP, Hannan AJ. Environmental enrichment ameliorates a motor coordination deficit in a mouse model of Rett syndrome-Mecp2 gene dosage effects and BDNF expression. *Eur J Neurosci* 2008;27(12):3342-50.
- [17] Lotan M, Shapiro M. Management of young children with Rett disorder in the controlled multi-sensory (Snoezelen) environment. *Brain Dev* 2005;27 Suppl 1:88-94.
- [18] Bumin G, Uyanik M, Yilmaz I, Kayihan H, Topçu M. Hydrotherapy for Rett syndrome. *J Rehabil Med* 2003;35(1):44-5.
- [19] Yasuhara A, Sugiyama Y. Music therapy for children with Rett syndrome. *Brain Dev* 2001;23 Suppl 1:82-84.
- [20] Wigram T, Lawrence M. Music therapy as a tool for assessing hand use and communicativeness in children with Rett Syndrome. *Brain Dev* 2005;27 Suppl 1:95-96.
- [21] Go T, Mitani A. A qualitative motion analysis study of voluntary hand movement induced by music in patients with Rett syndrome. *Neuropsychiatr Dis Treat* 2009;5:499-503.

2 Case study

2.1 Material and methods

2.1.1 Participant

Our participant was a girl from Germany, born in 2001 as the first child of healthy unrelated parents. Pregnancy was uneventful; delivery occurred at 41+3 weeks; meconium stained amniotic fluid was noted. At birth, her head circumference (OFC) was between the 10th and 25th percentile. Birth weight was at the 4th percentile and height at the 10th percentile. At the age of 22 months the girl was clinically diagnosed with classic RTT and genetic testing identified a p.R168X mutation in *MECP2*. Genetic testing of the parents revealed that the mutation had occurred spontaneously.

2.1.2 Material

The data for this case report is based on home videos, which were recorded by the family for their personal archive and were donated to the work group "Developmental Physiology and Developmental Neurology" at the Institute of Physiology, Medical University of Graz. The video footage was made during typical family routines (such as play situations, feeding, bathing, dressing) and special events (such as Christmas, visitors, excursions). The girl was recorded either alone - with or without objects in her immediate environment - or in interaction with or manipulation by the caregivers. The different settings were comparable throughout all months though age- specifically adapted.

2.1.3 Procedure

For the analysis we selected only those sequences in which at least one hand was clearly observable. Thus, our data base consisted of 267 video sequences, recorded at an age from 5 to 52 weeks. The total duration of all sequences was 365 minutes (6 hours and 5 minutes) ranging from 10 seconds to 4 minutes.

After some training sessions, the author analysed and meticulously documented all hand movements and postures. Afterwards the analysis was reviewed by the supervisor and discussed in case of disagreement until final agreement was obtained.

The rate of consistency of a pattern was defined by the percentage of sequences in which

the specific pattern was observed in at least one hand. Thus, a 100% consistency of a specific patterns refers to the occurrence of this pattern in at least one hand in each sequence of the month.

We defined 19 normal and 12 abnormal hand patterns and coded them as follows:

2.1.3.1 Description of patterns

2.1.3.1.1 Normal

Athetoid finger movements: Some fingers move in isolation and variably. The speed is slow. Wrist movements may accompany the finger movements.

Body weight support: The weight of the thorax and the shoulders is supported by both arms. Three different hand postures during body weight support were coded: (1) Support on the open hand: The fingers are extended and the palm is in contact with the ground (Figure 2.1). (2) Support on the half open hand: The fingers are extended in the metacarpophalangeal joint and flexed in the proximal interphalangeal joint. Thus, the palm of the hand and the distal phalanges are in contact with the ground (Figure 2.2). (3) Support on the fist: All fingers are flexed and the tips are in contact with the palm of the hand. The heel of the hand and the intermediate phalanges of the fingers are in contact with the ground (Figure 2.3).

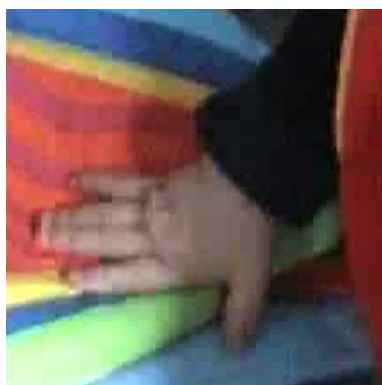


Figure 2.1: Support on open hand (videoprint).

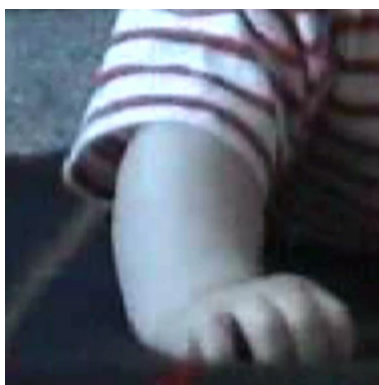


Figure 2.2: Support on half open hand (videoprint).

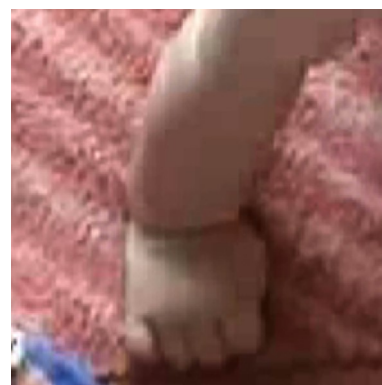


Figure 2.3: Support on fist (videoprint).

Fiddling: The fingers are semiflexed and make contact with a surface, the cloth or an object. Subsequently, small movements of the fingers occur.

Fisting: Fisting was subcategorised as: (1) Loose fisting: The fingers are moderately flexed towards the palm of the hand; the tips are not in contact with the palm (Figure 2.4). (2) Moderate fisting: The fingers are flexed towards the palm of the hand; the tips touch the palm (Figure 2.5). (3) Stiff fisting: The fingers are flexed and are firmly pressed towards

the palm (Figure 2.6).



Figure 2.4: loose fisting (videoprint).



Figure 2.5: moderate fisting (videoprint).



Figure 2.6: stiff fisting (videoprint).

Grasping: The half-open hand comes in contact with an object. Thereafter, the fingers are flexed and the object is enclosed.

Hand-to-hand movements: Both hands are brought together and the fingers of both hands touch, stroke and grasp each other.

Hand-to-mouth movements: The hand is led into the open(ing) mouth through flexion of the elbow and endorotation of the shoulder. The fingers can either be flexed, semiflexed or extended; sometimes only one finger is put into the mouth.

Index finger pointing: The index finger of the hand is extended while the other fingers are flexed or semiflexed.

Keeping an object in the hand: An object is enclosed by the fingers and kept in this position for at least 10 seconds.

Normal thumb adduction and endorotation: The thumb is moderately endorotated, adducted and flexed. The tip of the thumb touches the centre of the palm. The other fingers are flexed and enclose the thumb (Figure 2.7).

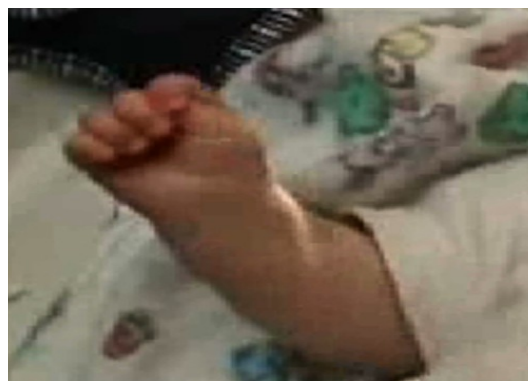


Figure 2.7: Normal thumb adduction and endorotation at 21 weeks (5 months) (videoprint).

Object manipulation: The fingers contact the surface of an object. Through variable finger movements the object's position is frequently changed.

Object-to-mouth movements: An object is enclosed by the fingers while the flexion of the elbow leads the hand to the open(ing) mouth.

Pulling: An object is grasped either with the whole hand or with a pincer grasp. Through flexion of the elbow the object is brought towards the participant.

Reaching: One or both arms extend to some object in the immediate environment. The fingers may contact the surface of the object. The eyes are directed towards the object (Figure 2.8).



Figure 2.8: Reaching at 22 weeks (5 months) (videoprint).

Pincer grasp: An object is grasped between the tips of the index finger and the thumb.

Tapping: The open hand and the forearm are elevated and subsequently hit the table. This procedure is repeated several times.

Transfer of objects: An object, which is kept in one hand is subsequently grasped by the other hand. Thereafter, the first hand releases the object, which is now transferred and kept in the second hand (Figure 2.9).



Figure 2.9: Transfer of an object from one hand to the other at 43 weeks (10 months) (videoprint).

Turning book pages: The page of a book is grasped and turned by a supination of the wrist.

Sometimes the hand pronates again and the open hand is placed on the open page of the book as if to fixate it.

Variable finger movements: The fingers are moved in a variable sequence, with variable speed and intensity. They may or may not be intentionally.

2.1.3.1.2 Abnormal

Abnormal hand-to-hand contact: The following two patterns were coded as abnormal hand-to-hand contact: (1) Both hands are repetitively brought together and immediately separated again. (2) The palms of both hands are brought together and the fingers enclose the contralateral hand. This posture is maintained at least during 4 seconds.

Abnormal superimposition of the hands: The palm of one hand is in contact with the ground, while the palm of the other hand is kept on the dorsal side of the first hand. This posture is maintained during at least 4 seconds. The fingers can be either flexed or semiflexed.

Abnormal thumb adduction and endorotation: The following two patterns were coded as abnormal thumb adduction and endorotation: (1) The thumb is extremely endorotated, adducted and flexed. The tip of the thumb touches the metacarpophalangeal joint of the 5th finger. The other fingers are flexed and enclose the thumb. (2) The thumb is either moderately or extremely endorotated, adducted and flexed towards the palm while the other fingers are either extended or semiflexed and do not enclose the thumb.

Abnormal thumb adduction and endorotation during support: The hand is positioned on the ground, supporting the weight of the shoulders and the thorax. The thumb is endorotated and adducted and "hidden" under the hand, while the other fingers are either extended or semiflexed (Figure 2.10).

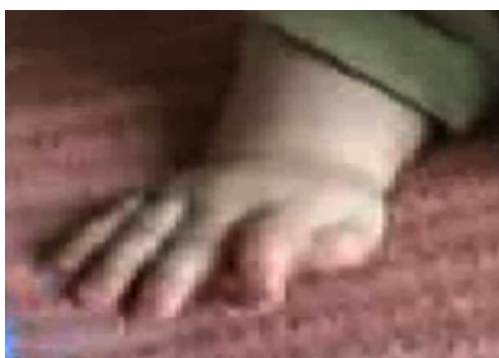


Figure 2.10: Abnormal endorotation and adduction of the thumb during body weight support at 24 weeks (6 months) (videoprint).

Abnormal wrist rotation: Uni- or bilateral (repetitive) pronation of the hand with simultaneous dorsiflexion of the wrist. Abnormal wrist rotation can either be seen as abnormal posture or as abnormal movement. Furthermore, repetitive opening and closing of the hand may co-occur.

Abnormal wrist rotation during support: Uni- or bilateral radial deviation of the wrist during body weight support.

Crossed fingers: The extended middle finger is placed over the extended index finger.

Lack of hand movements: Hardly any movements are performed with the hand. Often a slumped posture of the arm or the whole body co-occurs.

Repetitive opening and closing of the hand: It starts with an open hand and extended fingers; all fingers are simultaneously flexed to a fist and are immediately stretched again. This movement is performed repetitively and at a fast pace.

Short tremulous movements: The hand and forearm show several rhythmical oscillations of high frequency and low amplitude. They are either coded as spontaneous tremulous movements (the infant alone) or they are occurring during manipulation by a caregiver. They may occur uni- or bilaterally.

Spread fingers: All fingers, including the thumb, are extended and maximally abducted.

Washing movements: Both hands are brought together and perform repetitive washing movements.

2.2 Results

2.2.1 Results per month

2.2.1.1 The 2nd month of life

5 to 9 weeks; 32 sequences, 45 minutes

2.2.1.1.1 Hand movements and postures

During the 2nd month of life, normal hand movements and postures were seen in all 32 sequences (100%). Abnormal hand movements and postures were present in 21 out of 32 sequences (66%). There was no hand preference in six out of 32 sequences (19%). The right hand was dominant in twelve (38%) and the left hand in eight (25%) out of 32 sequences. In the remaining six sequences hand preference could not be analysed as either the right or the left hand was not accessible for observation.

Normal behaviour

The predominant normal hand activity during the 2nd month of life were athetoid finger movements, which occurred in 23 out of 32 (72%) sequences, equally often in both hands. Fisting was the predominant posture with an occurrence of 22 out of 32 episodes (69%); it was further classified into stiff, moderate or loose fisting. No hand preference was observed for stiff and moderate fisting, whereas loose fisting was mainly performed with the right hand (75%).

From 5 weeks onwards the girl showed endorotation and adduction of the thumb as a normal posture during fisting in five out of 32 sequences. The right hand seemed to be predominant for this posture as it was involved in all five sequences, whereas the left thumb was only once endorotated and adducted during fisting. A grasp reflex was observed in the right hand during the 7th week of life. From 7 weeks onwards the girl performed first movements to the midline by bringing her hands to the mouth in four out of 32 sequences (13%) (Figure 2.11). At the same time she started fiddling with the right hand, followed by the left hand 3 days later. By the end of the 2nd month variable finger movements were observed, first emerging in the right hand at 9 weeks but subsequently also performed by the left hand.



Figure 2.11: First hand movements to midline at 7 weeks (videoprint).

Abnormal behaviour

From 5 weeks onwards the girl presented short tremulous movements of the arm, mostly involving the forearm. The six sequences recorded during the 5th week of life showed short tremulous movements in four sequences (67%). In all episodes, the abnormal movements occurred during manipulation by the caregiver such as washing, bathing, drying and dressing. This abnormal behaviour during manipulation was seen in two further sequences between 6 and 9 weeks. In four out of six episodes (67%) it occurred bilaterally.

At the beginning of the 6th week of life, the girl demonstrated first short tremulous movements when she was not manipulated. These movements were observed firstly in the right arm; a week later they also occurred in the left arm. In contrast to the tremulous movements during manipulation, short spontaneous tremulous movements occurred either in the right or the left arm but never bilaterally.

The first abnormal posture was seen at 7 weeks, when the girl's thumb was endorotated and adducted although all other fingers were extended. This posture was shown in six out of 32 sequences (19%) and occurred mainly in the right hand (83%). Four out of 32 sequences (13%) were characterised by a lack of hand movements, co-occurring with either a slumped body posture (once) or a stiff body posture (3 times); the latter was also associated with stiff fisting. These peculiarities were observed either during manipulation or when the girl was kept in the caregiver's arms.

2.2.1.1.2 Additional findings

Normal

By the end of the 7th week the girl managed to keep her head in midline, which corresponds to normal motor development. Furthermore, normal wiggling oscillating arm movements

were seen twice and saccadic arm movements once.

Peculiar

During six sequences the girl was in an asymmetric tonic neck posture, during which her "occipital" hand was more active than her "facial" hand. Typically, the opposite is observed. A slumped body posture was observed once and was accompanied by a lack of movements in the left hand, while the right hand performed only a few athetoid movements.

In three out of 32 sequences (9%), a stiff body posture (Figure 2.12) was seen which was associated with a lack of movements in the right hand and short tremulous movement in the left arm (twice). In two out of three sequences, the girl was manipulated by the a caregiver while bathing.

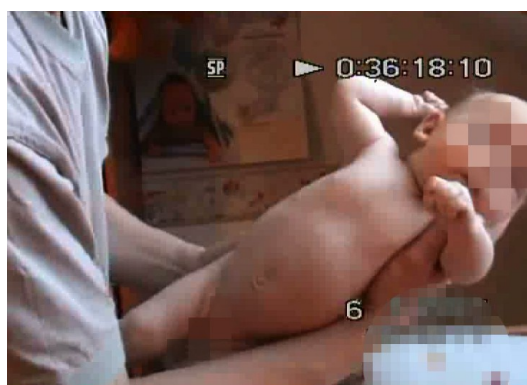


Figure 2.12: Stiff body posture during manipulation by a caregiver (videoprint).

2.2.1.2 The 3rd month of life

10 to 13 weeks; 19 sequences, 25 minutes

2.2.1.2.1 Hand movements and postures

During the 3rd month of life, normal hand movements and postures were seen in all 19 sequences (100%). Abnormal hand movements and postures occurred in 13 out of 19 sequences (68%). The right hand was predominant in ten (53%) and the left hand in five (26%) out of 19 sequences. There was no hand preference in three out of 19 sequences (16%) and once, hand preference could not be analysed.

Normal behaviour

The predominant normal hand movements were still athetoid finger movements in 14 out of 19 sequences (74%), followed by variable finger movements in twelve out of 19

sequences (63%); at no time there was a hand preference for these activities. Fiddling was no longer observed during the 3rd month of life. Fisting remained the predominant posture with an occurrence of 13 out of 19 sequences (68%). Endorotation and adduction of the thumb decreased and was only seen once during moderate fisting. A grasp reflex was seen once in the left hand.

Grasping occurred for the first time at 10 weeks, emerging in the right hand; two weeks later it was also performed by the left hand. During the 3rd month, the right hand was predominantly used for this movement (80%).

Reaching was not observed before the end of the 3rd month, however, never an object was provided. Only at 13 weeks, reaching occurred with the right hand although again no object was provided. Hand-to-mouth movements increased to seven out of 19 sequences (37%). Bilateral movements to midline, such as hand-to-hand contacts, were never observed.

Abnormal behaviour

The abnormal endorotated and adducted posture of the thumb increased from 19% during the 2nd month to 42%, and again occurred predominantly in the right hand (88%). Compared to the 2nd month, there was a decrease in short tremulous movements; they were observed in three out of 19 sequences (16%). Once, these tremulous movements were seen during forceful manipulation during bathing and co-occurred with stiff fisting and a stiff body posture; in the remaining two episodes the tremulous arm movements occurred spontaneously.

Three out of 19 sequences (16%) were characterised by a lack of hand movements, whereas twice both hands did not move. Such episodes were accompanied by a slumped body posture. Stiff fisting still occurred in 16% and was only performed during manipulation by the caregiver.

2.2.1.2.2 Additional findings

Peculiar

A stiff body posture was observed twice, once co-occurring with stiff fisting and short tremulous movements during bathing. A slumped body posture was seen once. Both abnormal postures were only present either during manipulation or interaction with the caregiver.

2.2.1.3 The 4th month of life

14 to 16 weeks; 16 sequences, 25 minutes

2.2.1.3.1 Hand movements and postures

During the 4th month of life normal hand movements and postures were observed in six (38%) and abnormal hand movements and postures in five (31%) out of 19 sequences. The girl showed no hand preference in four out of 19 sequences (25%). Once, a hand preference could not be analysed.

Normal behaviour

The predominant normal hand movements during the 4th month of life were variable finger movements (Figure 2.13) with an occurrence of 13 out of 16 sequences (81%), most of the time performed bilaterally. Athetoid finger movements decreased from 74% during the 3rd month of life to 25% of the sequences now. There was no hand preference for both movements.

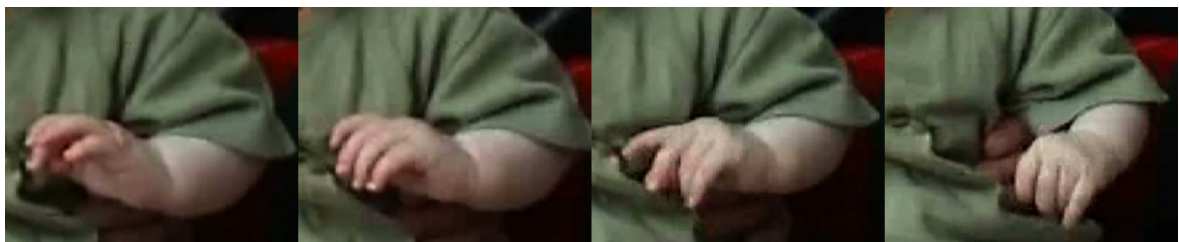


Figure 2.13: Variable finger movements at 16 weeks (videoprint).

Grasping increased to 56%, compared with 21% during the previous month. By contrast to the 3rd month, there was no hand preference for grasping. Reaching occurred in six out of 16 sequences (38%) and was mainly performed with the right hand (75%). In five of these sequences the girl was in supine and an object was provided. In four out of 16 sequences (25%), hand-to-mouth movements were observed, with no side preference.

Loose fisting still occurred in 13% of the sequences with no hand preference, whereas moderate fisting decreased to 50% of the sequences and was most of the time performed with the right hand (64%). Stiff fisting, which had been observed three times during the 3rd month, was never seen. Endorotation and adduction of the thumb during fisting was present in 31% of the sequences.

First object manipulations and object-to-mouth movements were observed at 15 weeks, both again occurring in a further sequence at 16 weeks. There was no hand preference for object-to-mouth movements, whereas object manipulations were only performed with the

right hand. At 16 weeks the girl started to keep objects in her hand without putting them to her mouth. This behaviour was mainly performed with the left hand (67%).

From 15 weeks onwards the girl was able to support her body weight when in prone either on the palm of her hand or on the fist. At one support, the thumb was endorotated and adducted.

Abnormal behaviour

Abnormal adduction and endorotation of the thumb increased from 42% during the 3rd month to 50% of the sequences. In two sequences, it was constantly present in the right hand. Spontaneous tremulous movements were observed twice, in the right arm. Abnormal adduction and endorotation of the thumb was coexistent in both episodes.

2.2.1.3.2 Additional findings

Peculiar

Episodes characterised by a lack of hand movements were seen twice when the girl was held on the caregiver's arm, both times associated with a slumped body posture. A stiff body posture occurred once at 16 weeks during bathing.

At one occasion, a long-lasting abnormal posture of the right arm was observed; it included adduction and exorotation of the shoulder, flexion of the elbow and maximal supination of the wrist (Figure 2.14).



Figure 2.14: Abnormal arm and hand posture at 16 weeks (videoprint).

2.2.1.4 The 5th month of life

18 to 22 weeks; 37 sequences, 42 minutes

2.2.1.4.1 Hand movements and postures

During the 5th month of life, normal hand movements and postures were observed in all 37

sequences (100%). Abnormal hand movements and postures were seen in 33 out of 37 sequences (89%). Right hand-use was preferred in 18 out of 37 sequences (49%). In ten out of 37 sequences (27%) the left hand was predominant. There was no hand preference in three out of 37 sequences (8%). In the remaining six sequences (16%), a hand preference could not be analysed.

Normal behaviour

The predominant normal hand movements during the 5th month of life were variable finger movements with an occurrence of 31 out of 37 sequences (84%). Grasping (Figure 2.15) decreased from 56% in the previous month to 43%, but remained the second most frequent normal hand movement. No hand-use preference was observed for both behaviours.



Figure 2.15: Grasping at 22 weeks (videoprint).

Fisting remained the predominant normal hand posture and was seen in 35% of the sequences. While there was an increase in moderate fisting, the occurrence of moderate fisting decreased. Moderate fisting was predominantly performed with the right hand (80%).

Reaching was observed in eight out of 37 sequences (22%) with no hand preference. Hand-to-mouth movements were present in 19% of the sequences, compared to 25% during the previous month. Hand-to-hand contact occurred in three out of 37 sequences (8%). At 20 weeks, the girl presented her first bimanual explorations of an object.

Compared to the previous month, object manipulations and object-to-mouth movements remained constant in occurrence, but were now also performed with the left hand (33%).

Keeping an object in the hand without putting it to the mouth occurred in 16% of the sequences and was most of the time performed with the right hand (71%). At the beginning of the 20th week, tapping was observed for the first time and was seen in one further sequence at 22 weeks, both times performed with the left hand. In 8% of the sequences the girl supported her body weight when in prone. This posture was often interrupted by an abnormal behaviour (see peculiar additional findings).

Abnormal behaviour

The predominant abnormal posture was still an abnormal adduction and endorotation of the thumb. While it had been observed in every second sequence during the 4th month of life, it was now present in 76% of the sequences, but did not show a side preference. In one sequence, this abnormal thumb posture was seen when the girl was in prone, supporting her body weight with all other fingers extended. Once, the girl showed still athetoid movements in her left hand, which are now age-inadequate. Short tremulous movements were observed once in the left arm. They occurred spontaneously and were accompanied by stiff fisting and a stiff body posture.

The following two abnormal movements emerged for the first time during the 5th month of life: (1) Fast and repetitive opening and closing of the hand was observed twice at 22 weeks, first emerging in the right hand but subsequently also performed by the left hand. It occurred either during interaction or manipulation by the caregiver, whereby during the latter it was continuously present. Both times, the thumb remained endorotated and adducted during opening and closing of the hand. (2) The other peculiarities were abnormal rotations of the wrist in five out of 37 sequences (14%) (Figure 2.16). They were twice associated with additional abnormal movements: At one time, monotonous and repetitive movements occurred in the right arm when the left wrist was abnormally rotated. The other time, abnormal wrist rotations co-occurred with repetitive opening and closing of the same hand. Two episodes of abnormal wrist rotations were seen when the infant was in prone position and tried to support her body weight.

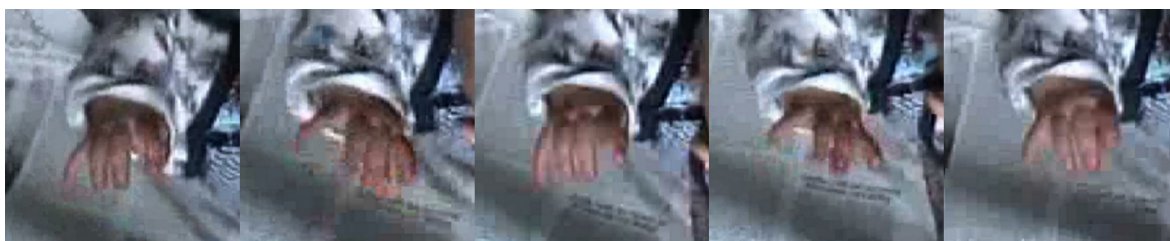


Figure 2.16: Abnormal rotations of the wrist at 23 weeks (videoprint).

2.2.1.4.2 Additional findings

Normal

Once, wiggling oscillating arm movements were observed.

Peculiar

A slumped body posture was seen in five out of 37 sequences (14%), of which four were

further characterised by a lack of hand movements. In three out of these five sequences (60%), the abnormal body posture occurred either during manipulation by the caregiver or interaction. As mentioned above, a stiff body posture was seen during one manipulation by the caregiver and was accompanied by short tremulous movements and stiff fisting.

Another abnormal body posture emerged at 18 weeks and was thereafter seen in seven out of 37 sequences (19%); the girl lifted arms and legs when in prone position and balanced her body weight on the trunk (Figure 2.17). This peculiar posture was interspersed by normal body weight support.



Figure 2.17: Abnormal body posture at 21 weeks (videoprint).

2.2.1.5 The 6th month of life

23 to 26 weeks; no data for week 27; 13 sequences, 20 minutes

2.2.1.5.1 Hand movements and postures

During the 6th month of life, normal hand movements and postures were seen in all 13 sequences (100%). Abnormal hand movements and postures were observed in eleven out of 13 sequences (85%). The right hand was predominant in five (38%) and the left hand in two (15%) out of 13 sequences. There was no hand preference in four out of 13 sequences (31%). Twice, a hand preference could not be analysed.

Normal behaviour

Variable finger movements remained the predominant hand activity with an occurrence of nine out of 13 sequences (69%). Athetoid finger movements were not longer observed.

Loose fisting was the predominant hand posture, performed in 4 out of 13 sequences (31%). Concordant to the previous month this posture increased, while moderate fisting declined to only 8% of the sequences. Neither stiff fisting nor endorotation and adduction

of the thumb were observed during this month.

Reaching occurred in three out of 13 sequences (23%) with no side preference. Grasping, which had decreased to 43% during the previous month, was observed in seven out of 13 sequences (54%). In four out of 13 sequences (31%) an object was held by the girl without putting it to the mouth. The same percentage applied to object manipulations. Grasping was performed with the left hand in 56% and holding and object in 60%. A month before, the right hand was predominantly used for these movements. Compared to the 5th month, there was no change in the occurrence of object-to-mouth movements (Figure 2.18). They were observed twice (15%) and performed equally often with both hands. Tapping was seen once with the right hand at 25 weeks, when the girl was in prone, and co-occurred with object manipulation.



Figure 2.18: Object-to-mouth movement at 23 weeks (videoprint).

At the beginning of the 26th week, object transfer from one hand to the other emerged. This behaviour is an important milestone in normal motor development and also is supposed to emerge during this period of life.

Abnormal behaviour

The predominant abnormal posture remained an abnormal endorotation and adduction of the thumb with an occurrence during all but three sequences (77%). In 20% this abnormal posture was present during body weight support.

Repetitive opening and closing of the hand increased by 4.5 fold and was observed in 23% of the sequences. Once, it co-occurred with abnormal rotations of the wrist in the same (i.e. left) hand (Figure 2.19). The occurrence of abnormal wrist rotations increased from 11% during the previous month to 31%. During two episodes, these abnormal wrist rotations co-occurred with abnormal endorotation and adduction of the thumb. There was no hand

preference for both peculiarities.



Figure 2.19: Repetitive opening and closing of the hand co-occurring with abnormal wrist rotations at 24 weeks (videoprint).

2.2.1.5.2 Additional findings

Normal

Once, wiggling oscillating arm movements were observed. Episodes of slumped or stiff body postures were not seen during this month. From 25 weeks onwards the girl increased her oral exploration of objects.

Peculiar

The abnormal posture of lifted arms and legs during prone position (described at 5 months) increased from 8% to 31%.

2.2.1.6 The 7th month of life

28 to 31 weeks; 22 sequences, 33 minutes

2.2.1.6.1 Hand movements and postures

Normal hand movements and postures were seen in all 22 sequences (100%). Abnormal hand movements and postures were observed in 18 out of 22 sequences (82%). The right hand was predominant in nine (42%) and the left hand in five (23%) out of 22 sequences. There was no hand preference in eight out of 22 sequences (36%).

Normal behaviour

The predominant normal hand movements during the 7th month of life were variable finger movements with an occurrence in 19 out of 22 sequences (86%). Tapping increased from 8% during the previous month to 73% and was therefore the second most predominant normal hand activity. In 67% tapping was performed with the right hand (Figure 2.20).



Figure 2.20: Tapping at 28 weeks (videoprint).

Moderate fisting was seen in eleven out of 22 sequences (50%) and was the predominant hand posture during the 7th month of life. Loose fisting was observed twice (9%) and stiff fisting once. Moderate and stiff fisting were predominantly performed with the right hand and loose fisting with the left hand. Twice, the thumb was adducted and endorotated during fisting.

Compared to the previous month, reaching increased and was shown in nine out of 22 sequences (41%) with no hand preference. Grasping occurred in nine out of 22 sequences (41%) and was mainly performed with the right hand (67%). The girl manipulated an object in four (18%) and kept an object in her hand without leading it to the mouth in seven (32%) out of 22 sequences. Hand-to-mouth movements occurred in four out of 22 sequences (18%). Twice, hand-to-face movements were observed in the right hand. Object-to-mouth movements increased from 15% during the previous month to 36% and were predominantly performed with the right hand. Hand-to-hand contact was seen in five out of 22 sequences (23%). Transfer of an object from one hand to the other was not observed during the 7th month of life.

Body weight support increased compared to the previous month with an occurrence of five out of 22 sequences (23%) on the palm of the hand, twice on the fist and twice on the half open hand.

Abnormal behaviour

Though the number of sequences in which an abnormal endorotation and adduction of the thumb could be observed decreased compared to the previous month, this feature still remained the predominant abnormal hand posture with an occurrence of twelve out of 22 sequences (55%). In five of them the abnormal thumb postures occurred when the girl supported her body weight on her fist.

The predominant abnormal hand movement was repetitive opening and closing of the hand which was shown in eight out of 22 sequences (36%). In three out of 22 sequences (14%), repetitive opening and closing of the hand was followed by or co-occurred with abnormal

rotations of the wrist. Once, an abnormal wrist rotation was performed as independent movement and once, it was observed as abnormal posture during body weight support. Two out of 22 sequences (9%) were characterised by a lack of hand movements. Short tremulous movements were observed once when the girl was manipulated by a caregiver and once occurring spontaneously.

Two abnormal hand postures emerged for the first time at 28 weeks: (1) The girl was in prone and kept the palm of one hand on the dorsal side of the other hand for several seconds (Figure 2.21). This peculiarity was seen in one further sequence until the end of the 7th month of life. (2) Once, the palms of the hands were put together - like praying - and held in this position for several seconds.

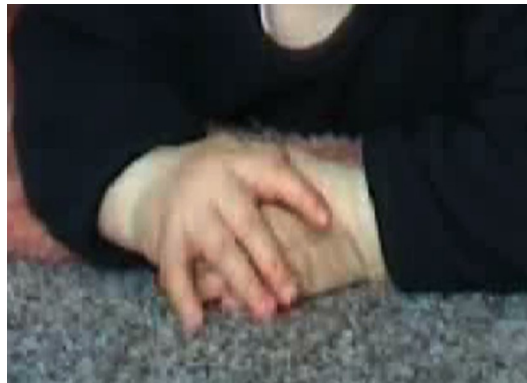


Figure 2.21: Abnormally prolonged superimposition of the hands at 31 weeks (videoprint).

2.2.1.6.2 Additional findings

Normal

Once, wiggling oscillating arm movements were observed.

Peculiar

Twice, the girl lifted arms and legs when in prone position and balanced her body weight on the trunk for several seconds.

2.2.1.7 The 8th month of life

32 to 35 weeks; 24 sequences, 33 minutes

2.2.1.7.1 Hand movements and postures

Normal hand movements and postures were performed in all 24 sequences (100%) and abnormal movements and postures in 13 out of 24 sequences (54%). The right hand was predominant in eleven (46%) and the left hand in twelve (50%) sequences. Once, the left

hand was not accessible for observation and therefore hand preference could not be analysed.

Normal behaviour

The predominant normal hand activity during the 8th month of life was grasping with an occurrence of 16 out of 24 sequences (67%), followed by reaching which was observed in 15 out of 24 sequences (63%). There was no hand preference for these movements.

Variable finger movements decreased from 86% during the previous month to 50% now. Tapping was observed in six out of 24 sequences (25%) and was preferentially performed with the right hand (86%). Hand-to-mouth movements occurred in eight out of 24 sequences (33%) and hand-to-face movements were seen once (Figure 2.22). The right hand was predominant for hand-to-mouth movements (80%).

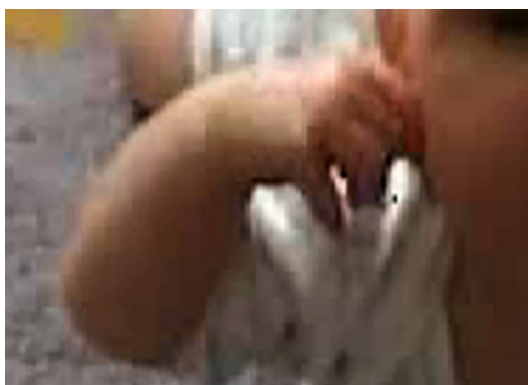


Figure 2.22: Hand-to-face movement at 35 weeks (videoprint).

Keeping an object in the hand without leading it to the mouth was shown once. In five out of 24 sequences (21%), the girl manipulated an object (Figure 2.23) and in four out of 24 sequences (17%) she led an object to her mouth. Whereas the right hand was preferentially used for object manipulation (67%), no hand preference was observed for object-to-mouth movements. Hand-to-hand movements decreased from 23% during the previous month to 13%. Transfer of an object from one hand to the other hand was performed in four out of 24 sequences (17%).

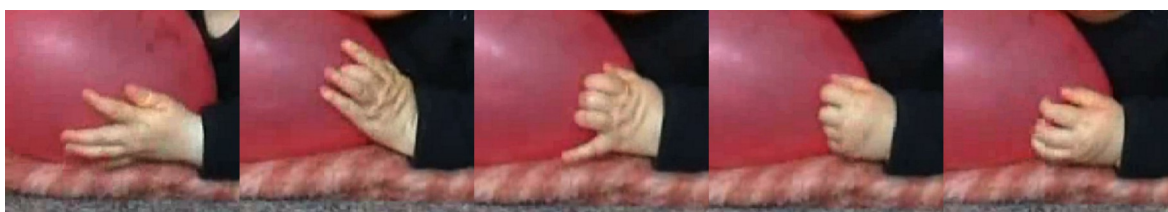


Figure 2.23: Object manipulation at 32 weeks (videoprint).

At the beginning of the 8th month of life, the girl pulled on an object for the first time. This movement was seen once and was performed with both hands. The first index finger pointing occurred at 33 weeks in the left hand.

Compared to the previous month, fisting decreased. Moderate fisting was seen only once in the left hand and loose fisting in three out of 24 sequences (13%); also in the left hand. Stiff fisting was not observed. Once the right thumb was endorotated and adducted during fisting.

Body weight support occurred mainly on the palm of the hand (58%) (Figure). Support on the first was seen in six (25%) and support on the half open hand in four (17%) out of 24 sequences. During body weight support, the right hand was rather fisted (67%) whereas the left hand was preferentially half open (75%).

Abnormal behaviour

Repetitive opening and closing of the hand was seen in nine out of 24 sequences (36%). In three out of 24 sequences (14%) it co-occurred with abnormal rotations of the wrist. An abnormal radial deviation of the wrist during body weight support was observed once in the left hand. Twice, the girl showed abnormal wrist rotations in the right hand. Spontaneous short tremulous movements were observed once in the right arm.

Abnormal adduction and endorotation of the thumb was the predominant hand posture during the 8th month of life with an occurrence in five out of 24 sequences (21%), predominantly in the left hand (83%). During body weight support, the thumb was abnormally adducted and endorotated in three out of 24 sequences (13%).

Once, the peculiar posture of abnormal and long lasting superimposition of the hands was observed.

First washing movements occurred at the beginning of this month and were seen in four out of 24 sequences (17%). Once, by the end of the 8th month of life the girl showed abnormal repetitive hand-to-hand movements.

2.2.1.7.2 Additional findings

Normal

Twice, remarkably good general body balance was noticed. At 35 weeks the girl achieved to balance her weight on the hands and the knees (crawling position) for the first time.

Peculiar

Once, the girl lifted her arms and legs and balanced her body weight on her trunk for

several seconds. By the end of week 33, repetitive nodding of the head first emerged. It was performed in one further sequence until the end of the 8th month. Asymmetric eye opening after blinking was first observed at 35 weeks of age.

2.2.1.8 The 9th month of life

36 to 40 weeks; 19 sequences, 32 minutes

2.2.1.8.1 Hand movements and postures

Normal hand movements and postures were seen in all but two sequences (89%) and abnormal hand movements and postures in eleven out of 19 sequences (58%).

The right hand was predominantly used in nine (47%) and the left hand in six (32%) out of 19 sequences. There was no hand preference in three out of 19 sequences (16%). Once, the right hand was not accessible for observation.

Normal behaviour

The predominant normal hand movements during the 9th month of life were grasping with an occurrence of nine out of 19 sequences (47%) followed by tapping in eight out of 19 sequences (21%). There was no hand preference for these movements. Reaching was observed in six out of 19 sequences (32%). Once, hand-to-mouth movements were performed with the right hand (Figure 2.24). Object manipulation was shown in three out of 19 sequences (16%), predominantly with the left hand. The girl led an object to her mouth in four out of 19 sequences (21%) (Figure 2.25). Hand-to-hand movements occurred once and transfer of an object from was seen twice. Variable finger movements, pulling on an object and index finger pointing were not seen during the 9th month of life.

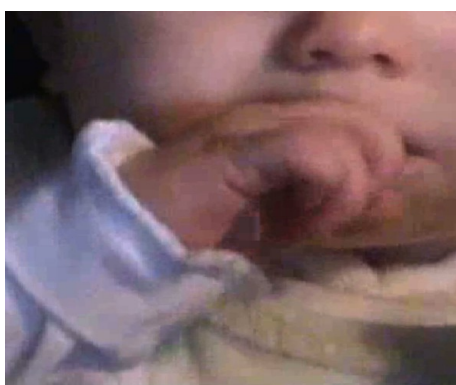


Figure 2.24: Hand-to-mouth movement at 36 weeks (videoprint).



Figure 2.25: Object-to-mouth movement at 36 weeks (videoprint).

Loose fisting was shown in four out of 19 sequences (21%) and moderate fisting in three

out of 19 sequences (16%). The right hand was preferentially used for loose fisting (75%) and the left hand for moderate fisting (67%). Stiff fisting was not observed during the 9th month of life.

Body weight support occurred on the palm of the hand in nine out of 19 sequences (47%) and once on the fist.

Abnormal behaviour

The predominant abnormal movements during the 9th month of life were washing movements with an occurrence of six out of 19 sequences (32%), followed by repetitive opening and closing of the hand in five out of 19 sequences (32%). In six out of 19 sequences (32%), fiddling was performed, which is rather unusual at this age. The right hand was predominant for this movement (86%).

Once, short tremulous arm movements occurred spontaneously on the right side. A general lack of movements was seen once in the left hand. Abnormal rotations of the wrist were observed twice. Both times, they were performed as independent movements and did not co-occur with repetitive opening and closing of the hand. Once, the thumb was abnormally endorotated and adducted in both hands. The abnormal superimposition of the hands was observed twice. Once, the girl put the palms of both hands together and maintained this praying-like posture for several seconds.

2.2.1.8.2 Additional findings

Normal

In two out of 19 sequences (11%) the girl managed to remain in crawling position during a whole sequence. At 36 weeks she achieved to crawl for the first time. This was seen in four further sequences until the end of the 9th month. From 37 weeks onwards the girl was able to sit unaided. At 40 weeks, the girl managed to keep her trunk in upright position, supporting her body weight on the knees.

Peculiar

Repetitive head nodding was observed in five out of 19 sequences (26%). Twice, asymmetric eye blinking and once, uni-lateral eye lid closing occurred. Once, the girl showed a general stiff body posture associated with a coarse tremor in the arms and seemingly rigid arms.

2.2.1.9 The 10th month of life

41 to 44 weeks; 37 sequences, 53 minutes

2.2.1.9.1 Hand movements and postures

During the 10th month of life, normal hand movements and postures were seen in all 37 sequences (100%). Abnormal hand movements and postures were observed in 20 out of 37 sequences (54%). There was no hand preference in six out of 37 sequences (16%). In 13 out of 37 sequences (35%) the right hand was preferentially used and in 17 out of 37 sequences (46%) the left hand was dominant. Once, the right hand was not accessible for analysis.

Normal behaviour

Grasping remained the predominant normal hand movement with an occurrence in 25 out of 37 sequences (68%). Object-to-mouth movements were seen in 15 out of 37 sequences (41%). Reaching (Figure 2.26) and object manipulation were performed equally often and were observed in twelve out of 37 sequences (32%). There was no hand preference for any of these movements.

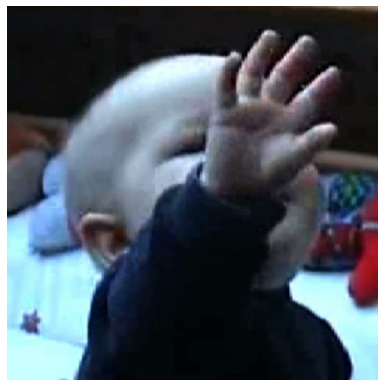


Figure 2.26: Reaching at 43 weeks. The right hand is reaching upwards while the left hand supports the body weight. This movement requires good balance control (videoprint).

Tapping occurred in ten out of 37 sequences (27%), predominantly in the right hand (77%). In nine out of 37 sequences (24%) an object was kept in the hand without putting it to the mouth. Hand-to-mouth movements occurred in three (8%) and hand-to-hand movements in four (11%) out of 37 sequences. The left hand was predominant for hand-to-mouth movements (75%). The girl transferred an object in eight out of 37 sequences (22%). Index finger pointing was preferentially performed with the right hand (67%) and was seen in six

out of 37 sequences (16%). Variable finger movements were observed in three out of 37 sequences (8%). Once, the girl pulled on an object with the right hand.

At 41 weeks the girl achieved to perform a pincer grasp, which was seen in three further sequences until the end of the 10th month. This movement was seen only in the right hand (Figure 2.27).



Figure 2.27: Pincer grasp at 43 weeks (videoprint).

By the end of the 10th month, at 44 weeks of age, turning of book pages occurred for the first time. Both hands were used equally often.

Moderate fisting was the predominant posture during the 10th month of life with an occurrence of ten out of 37 sequences (27%). It was mainly seen in the left hand (73%). Loose fisting was observed in three out of 37 sequences (8%) and stiff fisting once in the right hand.

Body weight support was shown on the palm of the hand in 16 (43%), on the half open hand in five (14%) and on the fist in six (16%) out of 37 sequences. Whereas the right hand was open most of the time (63%), the left hand was predominantly fistled (83%) during body weight support.

Abnormal behaviour

The predominant abnormal hand movements during the 10th month of life were abnormal rotations of the wrist, repetitive opening and closing of the hand and washing movements with an occurrence of five out of 37 sequences (14%). Abnormal rotations of the wrist did not co-occur with repetitive opening and closing of the hand or body weight support. Abnormal wrist rotations were predominantly performed with the right hand (83%).

Abnormal endorotation and adduction of the thumb was the predominant hand posture and was observed in six out of 37 sequences (16%). It occurred in the left hand in 71%. Twice, age-inadequate fiddling was shown with the left hand. The abnormal superimposition of the hands - when the palm of one hand was kept on the dorsal side of the other for several second - was seen twice. Once, the palms of both hands were brought together and kept in

this posture for several seconds. Repetitive hand-to-hand movements were shown once. At 42 weeks, spontaneous short tremulous movements were observed in the right arm.

In five out of 37 sequences (14%), the girl showed a lack of movements. This predominantly affected the left hand (63%) and was twice associated with a general slumped body posture.

A new abnormal movement pattern emerged at 44 weeks: The girl kept the middle finger of the left hand crossed over the index finger during support.

2.2.1.9.2 Additional findings

Normal

Twice, wiggling oscillating shoulder movements were observed.

At 41 weeks, the girl managed to stand for the first time with support.

Peculiar

Repetitive head nodding was observed in seven out of 37 sequences (19%). It was once associated with abnormal protrusion of the tongue. Abnormal tongue protrusion occurred in two further sequences until the end of the 10th month.

Twice, a slumped body posture was seen and was associated with a lack of movements in both hands.

At 43 weeks, general body balance was noted to get more unstable and by the end of the 10th month crawling seemed to be less coordinated than before.

2.2.1.10 The 11th month of life

45 to 48 weeks, no data for weeks 45 and 46; 21 sequences, 26 minutes

2.2.1.10.1 Hand movements and postures

During the 11th month of life, normal hand movements and postures were seen in all 21 sequences (100%). In 16 out of 21 sequences (78%), abnormal hand movements and postures could be observed. The right hand was predominant in eight (38%) and the left hand in five (24%) out of 21 sequences. There was no hand preference in six (29%) out of 21 sequences. Twice, a hand preference could not be analysed.

Normal behaviour

The predominant normal hand movement during the 11th month of life was grasping with an occurrence in 17 out of 21 sequences (81%). Index finger pointing increased from 16%

during the previous month to 43% now, and was therefore the second most common movement pattern. It was only observed on the right side (Figure 2.28).



Figure 2.28: Index finger pointing at 47 weeks (videoprint).

Reaching was seen in seven out of 21 sequences (33%) and was preferentially performed with the right hand (67%). The girl manipulated an object in six out of 21 sequences (29%), also predominantly with the right hand (67%). Object-to-mouth movements were seen twice and hand-to-mouth movements in three out of 21 sequences (14%). For both movements, the left hand was preferentially used. In three out of 37 sequences (14%) the girl put her hand to her face. Pulling an object and transfer of an object were seen once. Tapping occurred in four out of 21 sequences (19%). Once, the girl grabbed an object with a pincer grasp. At 47 weeks, the girl achieved to perform unilateral hand opening while she kept a toy in both hands.

Loose fisting was observed in three out of 21 sequences (14%). The same number applied for moderate and stiff fisting. Whereas the right hand was predominant for loose fisting (67%), stiff fisting was performed preferentially (75%), and moderate fisting only with the left hand.

Body weight support mainly occurred on the palm of the hand (52%). In three out of 21 sequences (14%) the fist was used for weight support.

Abnormal behaviour

The predominant abnormal hand movement during the 10th month of life remained repetitive opening and closing of the hand with an occurrence of three out of 21 sequences (14%). A lack of hand movements could also be observed in three out of 21 sequences (14%). Abnormal wrist rotations as independent movements were seen once in the left hand. Abnormal radial deviation of the wrist during weight support occurred in four out of

21 sequences (19%), and only in the left hand. Once, spontaneous short tremulous movements were observed in the left arm.

The predominant abnormal hand posture remained an abnormal adduction and endorotation of the thumb, which was shown in ten out of 21 sequences (45%). It occurred in the left hand in 64%. Twice, the girl kept her thumb in endorotated and adducted position during body weight support, while the other fingers were extended. Keeping both palms together for several seconds was seen once. In five out of 21 sequences (24%) the middle finger and the index finger of the left hand were crossed during weight support. This posture was never seen in the right hand (Figure 2.29).



Figure 2.29: Crossed fingers during crawling at 47 weeks (videoprint).

Two new peculiarities arose during the 11th month of life: (1) At 47 weeks, the fingers were kept in abnormally spread position during body weight support. This peculiarity occurred in one further sequence until the end of the 11th month. (2) At the same age, the girl showed manipulation of an object with spread fingers. This abnormal movement was also seen in one further sequence until the end of the 11th month.

Once, the girl manipulated an object without performing any fine manipulation, *i.e.* she did not perform finger-thumb adduction. Another peculiar situation was when the girl grasped and explored decoration sand with pincer grasps but unexpectedly did not put the sand into her mouth.

2.2.1.10.2 Additional findings

Peculiar

A generally slumped body posture was observed in three out of 21 sequences (14%) and was twice associated with a lack of movements in both hands (Figure 2.30). Twice, the girl

maintained a very stiff body posture while she was manipulated by the caregiver.



Figure 2.30: Slumped body posture at 47 weeks (videoprint).

Repetitive head nodding was seen in three out of 21 sequences (14%). Twice, a trunk instability during standing and a generally weakened body balance was noticed.

2.2.1.11 The 12th month of life

49 to 52 weeks; 27 sequences, 31 minutes

2.2.1.11.1 Hand movements and postures

During the 12th month of life, normal hand movements and postures were seen in 26 out of 27 sequences (96%) and abnormal hand movements and postures in 21 out of 27 sequences (78%). The right hand was preferentially used in 15 out of 27 sequences (56%). The left hand was dominant in seven out of 27 sequences (26%). In four out of 27 sequences (15%), no hand preference was observed and once the left hand was not accessible for analysis.

Normal behaviour

Grasping remained the predominant normal hand movement with an occurrence of 16 out of 27 sequences (59%), followed by reaching in eight out of 27 sequences (30%). Index finger pointing was seen in seven out of 27 sequences (26%), mainly in the right hand (75%). Variable finger movements occurred twice. In four out of 27 sequences (15%), tapping was performed.

Hand-to-mouth movements were observed in four (15%) and hand-to-hand movements in three (11%) out of 27 sequences. In five out of 27 sequences (19%), the girl manipulated an object. Twice, an object was lifted with pincer grasp. Turning of book pages (Figure

2.31) was seen twice, yet it seemed to happen with less muscle power than during the 10th month of life.



Figure 2.31: Turning the pages of a book at 50 weeks (videoprint).

Both loose and moderate fisting occurred in four out of 27 sequences (15%). Stiff fisting was observed once in the right hand. Body weight support was performed mainly on the palm of the hand (37%) or on the fist (22%). Only once, the right hand was half open during weight support.

Abnormal behaviour

Repetitive opening and closing of the hand remained the predominant abnormal hand movement with an occurrence of five out of 27 sequences (19%). It was preferentially performed with the right hand (67%). Abnormal rotations of the wrist were seen five times during the 37 sequences (11%); three times they co-occurred with repetitive opening and closing of the hand. Repetitive hand-to-hand movements were shown once and washing movements in three out of 27 sequences (11%). Age-inadequate fiddling occurred twice in both hands. The same applies to a general lack of hand movements, which was also observed twice in both hands. In seven out of 27 sequences (26%), the girl kept her thumb in endorotated and adducted position. This abnormal posture also occurred once in the left hand during body weight support. Twice, the middle finger and the index finger of the left hand were crossed during weight support.

A new abnormal finger position was shown at 51 weeks: The small finger was maximally abducted while the other fingers were in normal position (Figure 2.32). Abnormal spreading of all fingers was seen twice and once, the girl manipulated an object with spread fingers.



Figure 2.32: Maximal abduction of the small finger at 51 weeks (videoprint).

2.2.1.11.2 Additional findings

Normal

At 50 weeks, the girls managed to walk two steps with support. This behaviour was seen once more at the end of the 12th month. Very good balance was noticed during sitting while grasping objects at the end of the 12th month.

Peculiar

A stiff body posture occurred in three out of 27 sequences (11%) and was once associated with stiff fisting. Twice, a slumped body posture was observed. Both times a lack of hand movements co-occurred. At 51 weeks, the girl showed a lack of head control co-occurring with a stiff body posture and strong washing movements when she was held in supine and then put backwards by the caregiver.

Once, the caregiver tried to encourage the girl to walk. She seemed frightened, unwilling to take a step and showed repetitive opening and closing of both hands. Crawling was qualitatively abnormal at 51 weeks.

2.2.2 Occurrence and consistency of patterns

Both normal and abnormal hand behaviours were present during each month of the observation period. Normal patterns occurred very consistently because the girl performed at least one normal hand movement or posture in at least one hand in each sequence from the 2nd until the 11th month of life. During the 12th month normal patterns were observed in 26 out of 27 sequences (96%) in only one sequence only abnormal behaviours were seen in both hands. In contrast, abnormal behaviours were less consistently occurring. In other words, considering both data per month and all data, normal patterns were observed in

more sequences than abnormal patterns. The highest consistency was during the 5th month of life, during which at least one abnormal pattern in at least one hand was seen in 33 out of 37 sequences (89%). The occurrence of abnormal hand behaviours showed high fluctuations and a bimodal distribution (Figure 2.33).

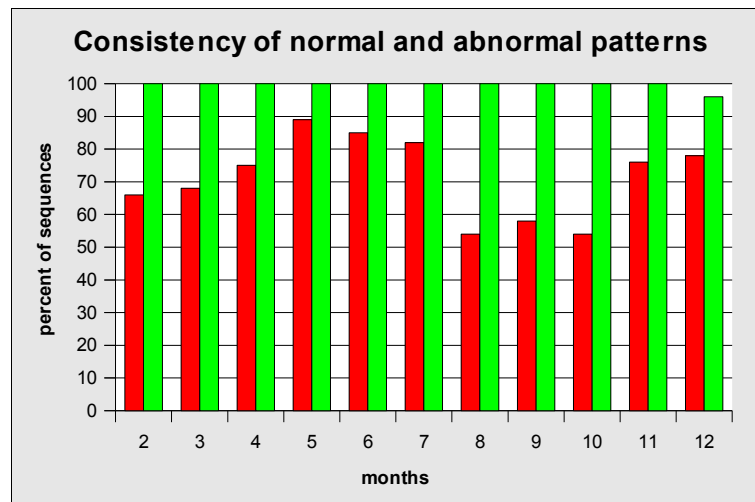


Figure 2.33: Rate of consistency (in percent of sequences per month) of normal and abnormal patterns. A 100% consistence refers to the occurrence of at least one normal/abnormal pattern in at least one hand in each sequence. Normal patterns in green, abnormal patterns in red.

The quantity of both abnormal and normal hand patterns increased over time ((Pearson correlation $r = 0.22$, $p < 0.001$); yet the increment was not continuous. Both graphics showed an increase until reaching the highest numbers in mid infancy. Afterwards there was a gradual decrease, although a second peak was observed during the 10th and 11th month, respectively. The quantity of different normal hand behaviours per sequence were lowest during the 2nd month of life (mean 2.7) and highest during the 7th month (mean 6.8). The maximum of abnormal patterns was reached at 6 months of age with an average of 2.5 abnormal behaviours per sequence. Thus, the monthly averages of different abnormal patterns per sequence were always below those of normal hand movements and postures (Figure 2.34).

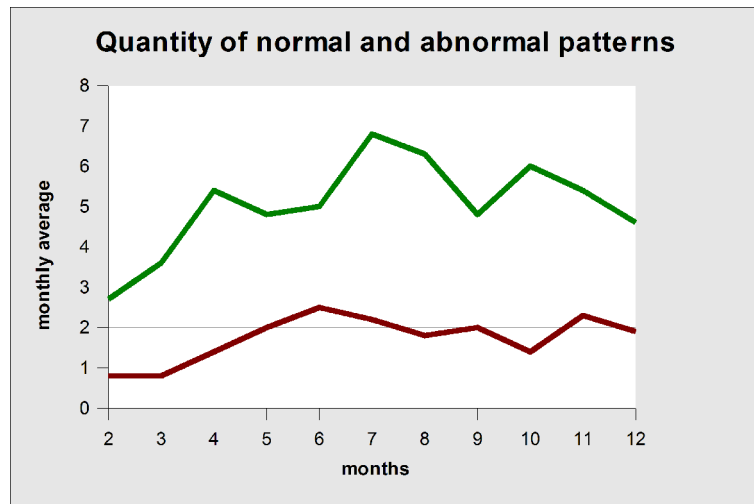


Figure 2.34: Quantity (as monthly average) of different normal and abnormal patterns per sequence. Normal behaviours in green, abnormal behaviours in red.

2.2.3 Hand preference

During 6 months of the observation period, the right hand was predominantly used for both normal and abnormal movements and postures, while the left hand was preferred only during the 8th and 10th month (Figure 2.35). Yet, the rates of laterality did not reach statistical significance.

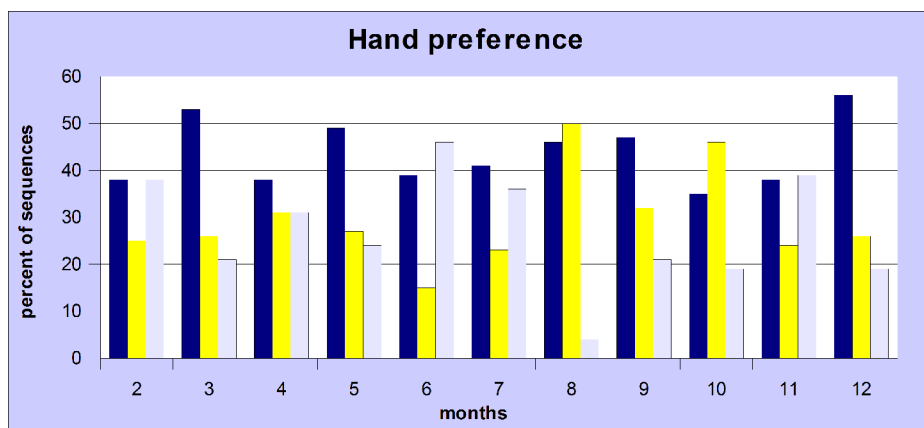


Figure 2.35: Hand preference for each month of the observation period. Right-hand preference in blue, left-hand preference in yellow. Light blue bars demonstrate the percentage of sequences in which there was no hand preference or hand preference could not be analysed.

The participant also showed a right-hand preference for some patterns during the first months of occurrence including reaching, grasping (Figure 2.36), object-to-mouth movements, object manipulation, index finger pointing and pincer grasp.

Additionally, there was a positive correlation between the numbers of normal and

abnormal behaviours in the right hand (Pearson correlation $r = 0.13$, $p < 0.05$).

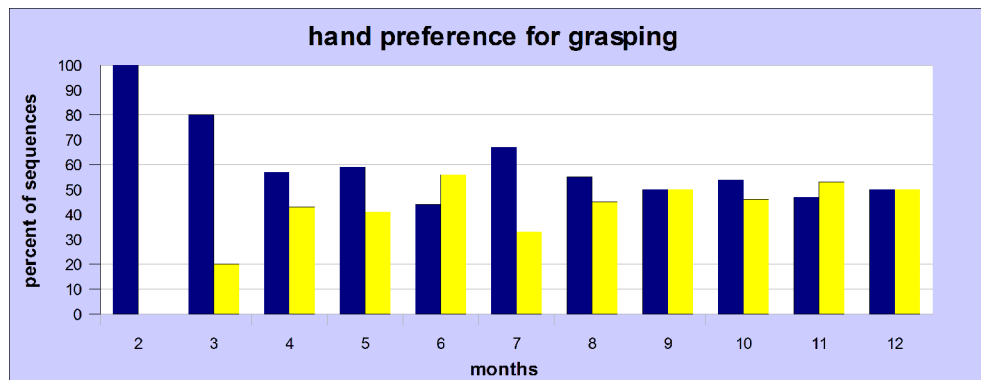


Figure 2.36: Hand preference for grasping (in percent of sequences per month). Right-hand preference in blue, left-hand preference in yellow.

2.2.4 Age-adequate hand functions

Athetoid finger movements were the predominant movements during the 2nd and 3rd month of life. Variable finger movements also occurred from the 2nd month onwards and were predominant after the 3rd month (Figure 2.37).

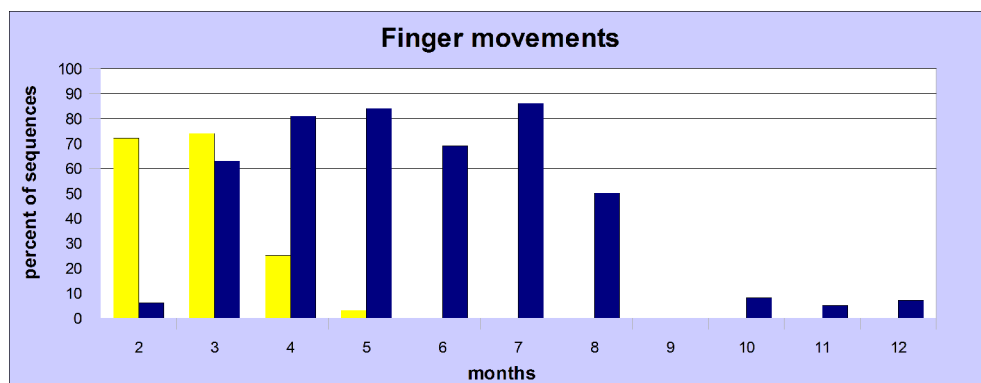


Figure 2.37: Rate of consistency (in percent of sequences per month) of athetoid finger movements (in blue) and variable finger movements (in yellow).

The girl showed a grasp reflex during the 2nd and 3rd month and first intentional grasping at 10 weeks (3 months) of age (Figure 2.38). During the first half of the observation period there was a right-hand preference for grasping, while no hand preference could be observed from the 8th until the 12th month of life (Figure 3).

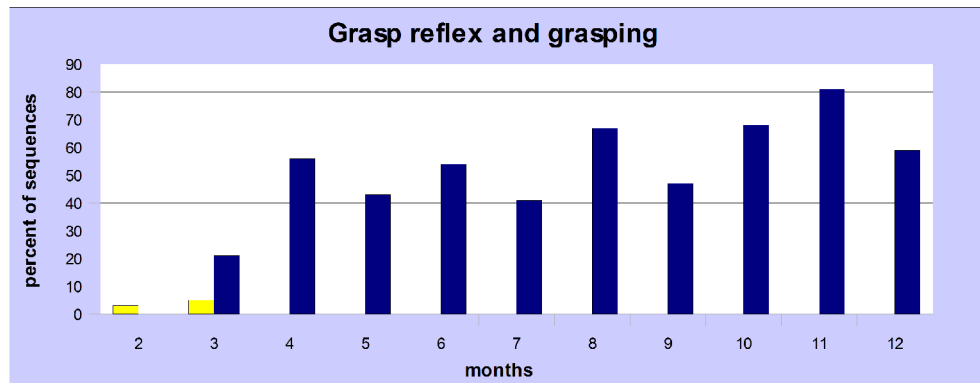


Figure 2.38: Rate of consistency (in percent of sequences per month) of grasp reflex (in yellow) and grasping (in blue).

Reaching emerged at the end of the 3rd month. At 14 weeks (4 months) the girl for the first time brought the hands together in midline and one week later, at 15 weeks, she started to manipulate objects and brought them to her mouth. The latter two movements had their highest rates of consistency during the 10th month. During the 5th month the first bimanual exploration of an object was observed. At 26 weeks (6 months) the girl was able to transfer an object from one hand to the other. Index finger pointing was seen for the first time at 33 weeks (8 months) and was preferentially performed with the right hand throughout the whole observation period (Figure 2.39).

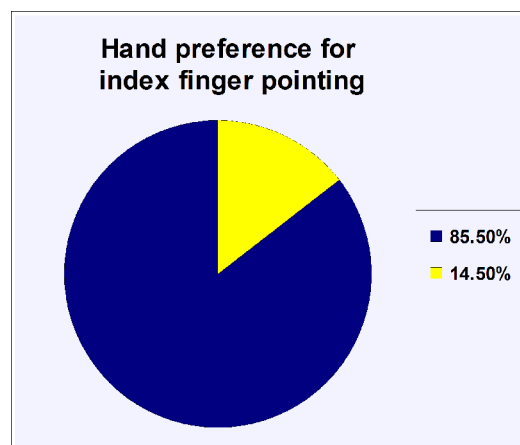


Figure 2.39: Hand preference for index finger pointing considering all 23 sequences in which this movement occurred. Right-hand preference in blue, left hand preference in yellow.

At the beginning of the 10th month a pincer grasp was observed for the first time and by the end of the month the girl achieved differentiated and coordinated bimanual movements - such as turning the pages of a book (Figure 3.30).

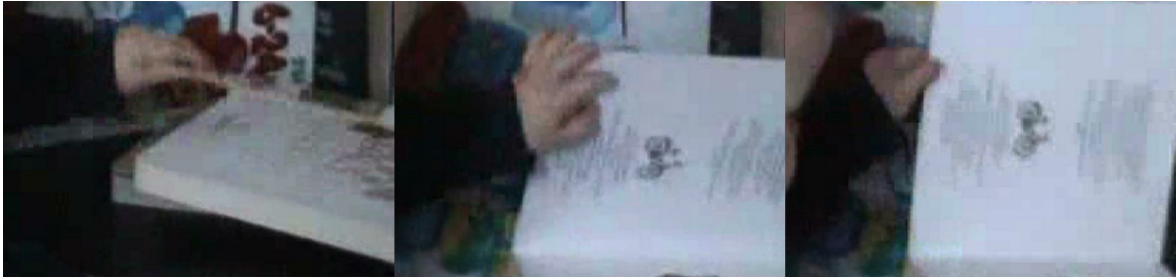


Figure 2.40: Turning the pages of a book at 44 weeks (10 months) (videoprint).

The presence of the different normal hand behaviours for each month are shown in table 2.1.

Pattern	Months											
	2	3	4	5	6	7	8	9	10	11	12	
Fiddling	●											
Grasp reflex	●	●										
Athetoid finger movements	●	●	●	●								
Fisting	●	●	●	●	●	●	●	●	●	●	●	
Hand-to-mouth movements	●	●	●	●	●	●	●	●	●	●	●	
Variable finger movements	●	●	●	●	●	●	●		●	●	●	
Reaching		●	●	●	●	●	●	●	●	●	●	
Intentional grasping		●	●	●	●	●	●	●	●	●	●	
Body weight support		●	●	●	●	●	●	●	●	●	●	
Manipulating object			●	●	●	●	●	●	●	●	●	
Object-to-mouth movements			●	●	●	●	●	●	●	●		
Hand-to-hand movements			●	●		●	●	●	●		●	
Tapping				●	●	●	●	●	●	●	●	
Transfer of objects					●		●	●	●	●		
Index finger pointing							●		●	●	●	
Pulling							●		●	●		
Pincer grasp									●	●	●	
Turning over pages									●		●	

Table 2.1: Occurrence of normal hand behaviours during the observation period. The presence of a specific pattern is marked with ● on a grey background.

2.2.5 Recurrent abnormal hand behaviours

We identified 12 different abnormal hand patterns (Table 2.2) of which some were almost continuously present throughout the whole observation period or showed high rates of occurrence. These recurrent abnormal behaviours included abnormal adduction and

endorotation of the thumb, short tremulous movements, lack of hand movements, repetitive hand opening and closing, abnormal wrist rotations, abnormal hand-to-hand movements or postures and washing movements.

<i>Patterns</i>	<i>Months</i>											
	2	3	4	5	6	7	8	9	10	11	12	
<i>Thumb adduction and endorotation</i>	●	●	●	●	●	●	●	●	●	●	●	
<i>Short tremulous movements</i>	●	●	●	●		●	●	●	●	●		
<i>Lack of hand movements</i>	●	●	●	●		●			●	●	●	
<i>Repetitive hand opening and closing</i>				●	●	●	●	●	●	●	●	
<i>Abnormal wrist rotations</i>				●	●	●	●	●	●	●	●	
<i>Not age-adequate fiddling</i>				●				●	●		●	
<i>Prolonged superimposition of the hands</i>						●	●	●	●	●		
<i>Prolonged praying-like hand posture</i>						●			●			
<i>Washing movements</i>							●	●	●		●	
<i>Repetitive hand-to-hand movements</i>							●	●	●		●	
<i>Fingers crossed during support</i>									●	●	●	
<i>Finger spreading (including object manipulation with spread fingers)</i>										●	●	

Table 2.2: Occurrence of abnormal hand behaviours during the observation period. The presence of a specific pattern is marked with • on a grey background.

2.2.5.1 Short tremulous movements

These rhythmical oscillations of high frequency and low amplitude in the hands and forearms were the first abnormal pattern during the observation period. This behaviour was seen for the first time at 5 weeks of age, when the girl's face was cleaned by a caregiver. From 6 weeks onwards these tremulous movements also occurred spontaneously when the girl was alone.

They occurred most often during the 2nd month of life and then gradually decreased with age ($p < 0.05$). While most of the time tremulous movements occurred spontaneously (Chi-Square, $p > 0.01$), such movements occurred during manipulation solely during the 2nd, 3rd and 7th month of life (Figure 2.41). Occasionally, this behaviour was associated with stiff fisting of the affected hand or with a stiff body posture.

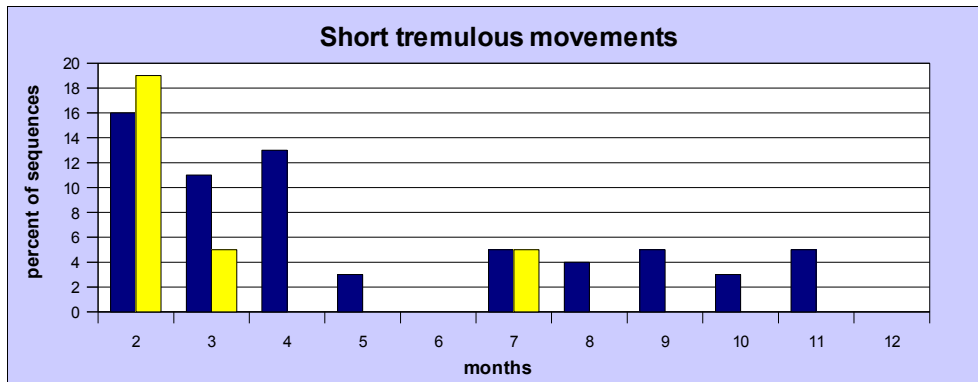


Figure 2.41: Rate of consistency (in percent of sequences per month) of short tremulous movements; spontaneously in blue and during manipulation in yellow.

2.2.5.2 Abnormal adduction and endorotation of the thumb

This unusual posture of the thumb was observed for the first time at 7 weeks (2 months), when the girl was in supine and alone. While the thumb was adducted and endorotated, the other fingers were extended (Figure 2.42).

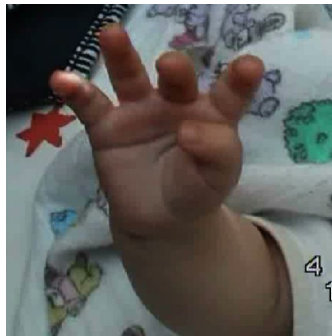


Figure 2.42: abnormal adduction and endorotation of the thumb at 7 weeks (2 months) (videoprint).

Later, this posture was also seen when the other fingers were flexed but in this case the maximal adduction and maximal endorotation led to a contact between the tip of the thumb and the metacarpophalangeal joint of the 5th finger. This abnormal thumb posture was the most consistent abnormal behaviour displayed during the whole observation period. It could be observed during each month though with fluctuations in the frequency of occurrence: The highest rates of consistency were found during the 5th month of life, i.e. in 76% of 37 sequences. During the 9th month of life, however, this pattern was seen in only 5% of 19 sequences (Figure 2.43). Considering all 267 sequences, the mean rate of consistency was 42% indicating that this unusual thumb posture was also the most frequent

abnormal pattern.

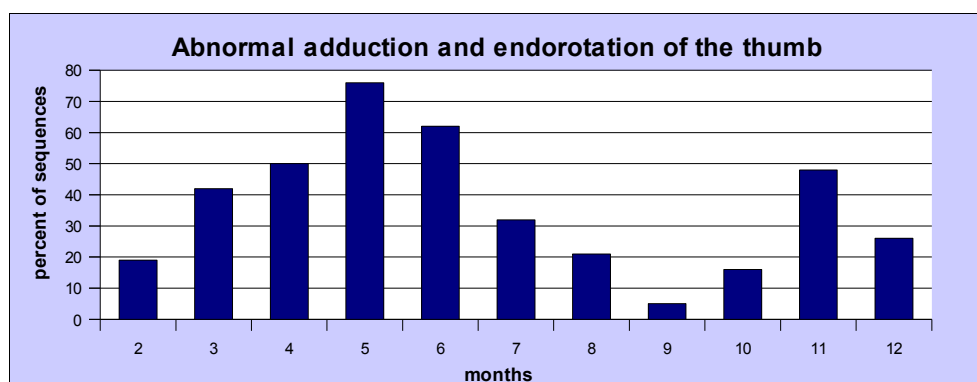


Figure 2.43: Rate of consistency (in percent of sequences per month) of abnormal adduction and endorotation of the thumb.

Although during the 8th month of life this behaviour was mainly observed in the left hand, no hand preference could be revealed considering all data.

Once the girl started to support her body weight on her hands when in prone position, she occasionally showed this abnormal thumb posture. In this case, the thumb was "hidden" under the hand while the other fingers were extended. This behaviour was seen for the first time during the 4th month of life and was thereafter continuously observed except during the 9th and 10th months. During the 4th and 5th month this posture was exclusively observed in the left hand; from 6 months onwards it also but rarely occurred in the right hand. Hence, the left hand preference remained throughout the observation period.

2.2.5.3 Lack of hand movements

A lack of hand movements was first obvious at 6 weeks (5 months) in the left hand when the girl was kept on a caregiver's arm. This behaviour was then observed nearly each month of the observation period except for the 6th, 8th and 9th month (Figure 2.44). The posture was often seen bilaterally and mostly associated with generally being quiet. On several occasions a slumped body posture was co-occurring; yet, during bathing lack of hand movements was associated with some stiffness and short tremulous movements. Initially lack of hand movements were only observed when the girl was either manipulated or kept on a caregiver's arm or lap. Later it also occurred during sitting and once during standing with support. Although during the 2nd month of life the right hand was affected more often, there was no hand preference for this behaviour considering all data.



Figure 2.44: Rate of consistency (in percent of sequences per month) of lack of hand movements.

2.2.5.4 Abnormal wrist rotations

An abnormal wrist rotation, characterised by uni- or bilateral (repetitive) pronation of the hand with simultaneous dorsiflexion of the wrist, was seen for the first time at 18 weeks (5 months) when the girl was alone, reaching upwards for toys. In this situation the behaviour occurred repetitively in the left hand. From the 5th month onwards this movement was observed throughout the whole observation period and had the highest rate of occurrence during the 6th month of life. During the 7th and 8th month it was only seen in the left hand and - considering all data - the left-hand preference remained throughout the observation period. Occasionally, this behaviour was co-occurring with a repetitive opening and closing of the hand, especially during the 7th, 8th and 12th month (Figure 2.45).

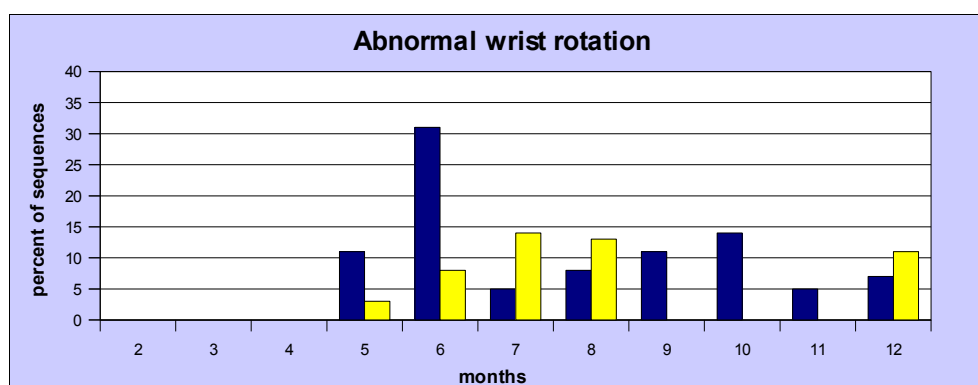


Figure 2.45: Rate of consistency (in percent of sequences per month) of abnormal wrist rotations (in blue). Yellow bars demonstrate the co-occurrence with repetitive opening and closing of the hand.

From 21 weeks (5 months) onwards the girl showed abnormal rotations of the wrist even if in prone position. In such a case, a radial deviation of the hand was observed. This posture was especially seen during the 11th month of life with an occurrence in 19% of 21 sequences. It was mainly performed with the left hand, while the right hand was involved

only once during the 5th month. During the 11th month, once the left hand was supinated and the girl supported her body weight on the dorsal side of the hand (Figure 2.46).



Figure 2.46: Abnormal wrist rotation in the left hand during body weight support at 47 weeks (11 months) (videoprint).

2.2.5.5 Repetitive opening and closing of the hand

These movements were seen for the first time at 22 weeks (5 months) of age in the right hand. In this situation, a caregiver interacted with the girl, providing a balloon which she occasionally grasped and manipulated. From the 5th month onwards the repetitive opening and closing of the hand (Figure 2.47) was observed during each month of the observation period. This behaviour rarely occurred when the girl was alone but rather when she was kept on the caregiver's arm or lap or when the caregiver interacted with her.

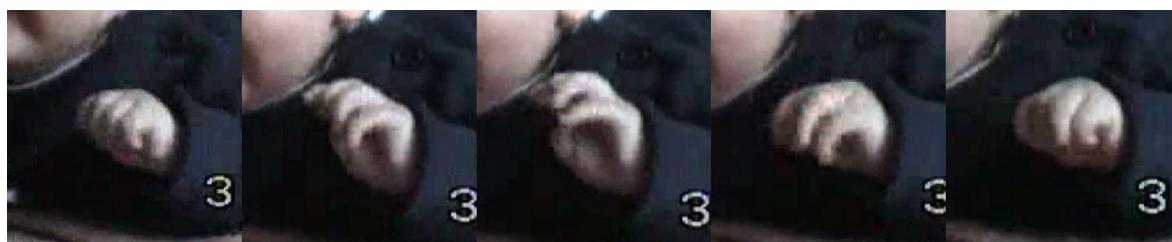


Figure 2.47: A sequence out of a episode of repetitive opening and closing of the hand at 26 weeks (6 months) (videoprint).

Most excessive was this pattern during bathing or manipulating. In addition, these movements were sometimes co-occurring with lifted arms and legs when lying in prone position. In such a situation the repetitive hand movements were always performed bilaterally.

The rates of consistency of repetitive hand opening and closing increased until reaching a maximum during the 7th and 8th month and then gradually decreased again (Figure 2.48).

The overall rate of consistency for this pattern was 14% of all 267 sequences. There was never hand preference for this behaviour.

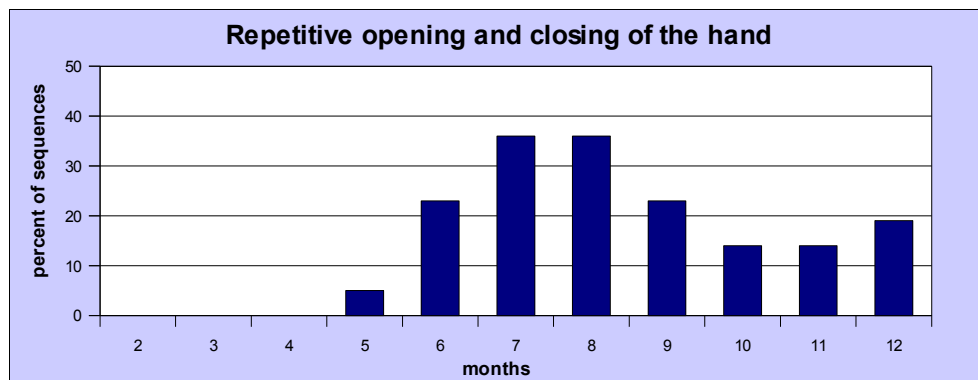


Figure 2.48: Rate of consistency (in percent of sequences per month) of repetitive opening and closing of the hand.

2.2.5.6 Abnormal hand-to-hand contact

Abnormal hand-to-hand contacts were characterised either as repetitive bringing together of both hands immediately followed by their separation or as unusual and prolonged (lasting at least 4 seconds) posture of the joined hands. The latter was seen for the first time during the 7th month of life: at 28 weeks, while the girl was in prone position and a caregiver interacted with her, she brought the palms of both hands together, enclosed with one hand the fingers of the other hand and kept this praying-like posture for several seconds (Figure 2.49). Three weeks later, by the end of the 7th month, an abnormal and prolonged superimposition of the hands was observed: the palm of one hand was on the ground, while the palm of the other hand was kept on the dorsal side of the first hand for several seconds (Figure 2.50).

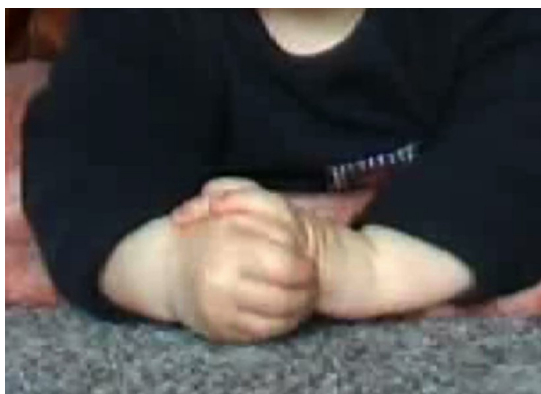


Figure 2.49: Abnormally prolonged praying-like position at 31 weeks (7 months) (videoprint).



Figure 2.50: Abnormally prolonged super-imposition of the hands at 35 weeks (8 months) (videoprint).

From the 7th until the 9th month these postures only occurred when the girl was in prone position, supporting her body weight on her forearms. Later, they were seen when the girl was sitting in a baby-chair during breakfast. While the praying-like position was only observed during the 7th and 10th month of life, abnormal superimposition of the hands occurred from the 7th until the 11th month with the highest rate of consistency during the 9th month (Figure 2.51).

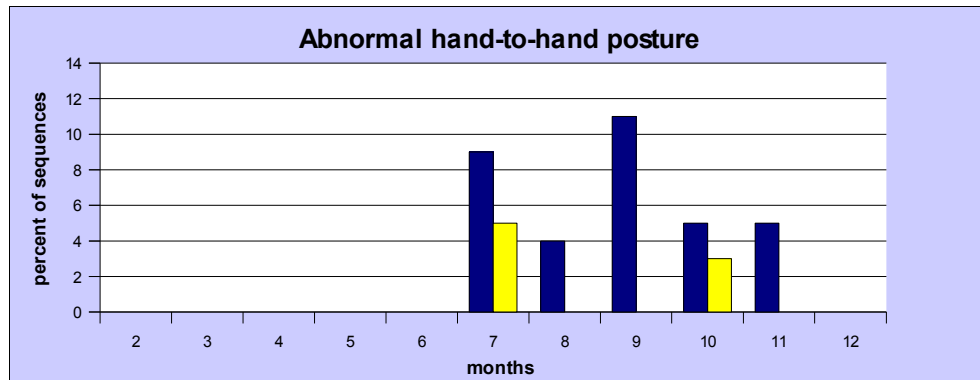


Figure 2.51: Rate of consistency (in percent of sequences per month) of abnormal hand-to-hand postures. Superimposition of the hands in blue, praying-like position in yellow.

Repetitive hand-to-hand movements were seen for the first time during the 8th month of life, during which they also had their maximum rate of consistency. Afterwards, they were observed throughout the rest of the observation period with exception of the 11th month. This behaviour was excessively performed when the girl was cleaned, during change of napkins and during crying.

2.2.5.7 Washing movements

Washing movements (Figure 2.52), which are so typical for RTT, were observed for the first time at 32 weeks (8 months). During the first two months of occurrence (8th and 9th month) they were mostly performed when the girl was alone and in prone position. Later, they were mainly seen during sitting or standing with support.



Figure 2.52: Washing movements at 43 weeks (10 months) (videoprint).

In some sequences this behaviour was interspersed by repetitive hand-to-hand movements or by superimpositions of the hands. At 40 weeks (9 months) washing movements were continuously present during a one-minute sequence. Once, at the age of 52 weeks (12 months), washing movements were performed excessively when the girl was first kept in supine and then put into prone at the caregiver's arms. At the same time she had a very stiff body posture and obviously lost head control.

After the first appearance, washing movements were continuously seen until the end of the observation period, with exception of the 11th month. The highest rate of consistency was during the 9th month during which washing movements occurred in 32% of 19 sequences (Figure 2.53).

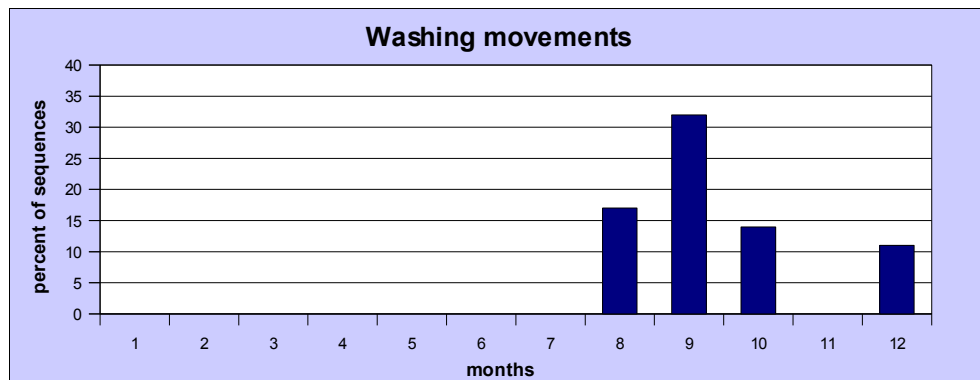


Figure 2.53: Rate of consistency (in percent of sequences per month) of washing movements.

3 Discussion

Although several retrospective studies have analysed the early development of patients with RTT^[1-15], our study was the first to focus on the development of both hand function and abnormal hand patterns during the first year of life in a girl who later was diagnosed with classic RTT. By meticulous analysis of 267 sequences obtained from family videos we found that both normal and abnormal hand patterns were present during each month of the observation period. This result is consistent with the results of others who revealed that normal and abnormal movements mingle before hand function is lost^[1-4]. Yet, the rates of consistency (in percent of sequences per month) of abnormal hand patterns always remained at a lower level than those of normal behaviours. In other words, we observed normal patterns in more sequences than abnormal behaviours. This contradicts our expectation that abnormal patterns would increase and normal patterns would decrease over time. The slight decrement in the consistency of normal hand movements and postures during the 12th month of life, which was co-occurring with an increase in the consistency of abnormal hand behaviours, might indicate that our suggestion is still valid, yet for a later age. This would be in agreement with several studies who revealed a mean age of loss of hand function at 18 months or later^[10, 16, 17].

While in healthy infants the quantity of different normal hand patterns increases with age^[18], our study participant showed an unusual development of normal behaviours. Although statistical analysis revealed that the amount of different patterns increased over time, we found that this increment was not continuous. In fact, the mean numbers of normal patterns per sequence increased until the 7th month of life but then continuously decreased again. Interestingly, the quantities of abnormal behaviours per sequence showed a similar pattern, although the monthly averages were always lower than those of normal behaviours and the maximum was reached already at 6 months of age. These findings might indicate that the ability to perform a variety of different movements and postures was gradually lost after mid-infancy.

During the 3rd to 5th, 7th, 9th and 12th month of life the right hand was preferentially used for both normal and abnormal movements and postures, while the left hand was only preferred during the 8th and 10th month. Furthermore we revealed a right-hand preference for some patterns during the first months of their occurrence such as reaching, grasping, object-to-

mouth movements, object manipulation, index finger pointing and pincer grasp. Yet, the rates of laterality did not reach statistical significance and we further need to consider, that hand preference in infancy has a low predictive character and laterality is commonly not developed before mid-childhood (see chapter 1.4.1 Normal hand function in infancy). Additionally, we found a positive correlation between the numbers of normal and abnormal behaviours in the right hand, which is consistent with the findings of Carter and colleagues, who revealed that most of their 144 study participant used the hand which was predominantly affected by stereotypies also to carry out purposeful movements^[19].

The occurrence of abnormal patterns during each month of the observation period corresponds to the reports of midwives and health visitors in a video study by Burford^[5]. They described unusual hand behaviours at different ages in several participants during the first year of life. Due to the lack of data of the first month of life, we could not validate the midwives' comments on abnormal hand behaviours in the early postnatal period. However, we observed the first abnormal pattern – short tremulous hand and arm movements – already at the beginning of the observation period (5 weeks). From 7 weeks onwards the girl occasionally showed an abnormal adduction and endorotation of the thumb. Considering the data of all twelve abnormal behaviours observed, this unusual thumb posture was the most consistent one as it was seen during each month. Additionally, it showed the highest frequency among all abnormal patterns with a mean rate of consistency in 42% of all 267 sequences. Interestingly, despite its consistency and high occurrence rates, this posture has not yet been described by any other researchers.

However, some of the abnormal patterns seen in our participant have also been reported in other retrospective video studies of infants who were later diagnosed with RTT^[1,4-7,9]. We observed repetitive opening and closing of the hands in an average of 14% of all 267 sequences. This feature was also identified in three out of four study participants by Kerr and colleagues^[1] and in two out of 22 infants in a study by Einspieler and colleagues^[6]. Yet, contrary to our participant who did not show this unusual movements before the 5th month, Einspieler and colleagues already observed this pattern during the first 6 months of life. Einspieler et al also reported excessive finger spreading in one of 22 participants during the first 2 months of life, which we could confirm in our participant; yet not before the end of the observation period, that is during the 11th and 12th month. During these two months we also observed excessively spread fingers during object manipulation, which has earlier also been described by Einspieler et al and Marschik et al^[4,6]. Occasionally, our participant

showed a maximal abduction of the 5th finger, while the other fingers were kept in normal position.

Abnormal rotations of the wrist were among the most frequently present abnormal patterns. These movements have earlier been described by several other researchers^[1,4-7]. However, co-occurrence with repetitive opening and closing of the hands as seen in our participant has not been reported so far. Consistent with Temudo, we also observed abnormal wrist rotations - especially endorotations of the wrist - during body weight support. We could further identify another abnormal feature which was equally described in Temudo's case study: From the 10th until the 12th month our participant occasionally twisted two fingers during crawling. Interestingly, Temudo observed this pattern only in the infant's left hand, which was also true for our participant^[7].

Short tremulous movements occurred throughout the whole observation period - with exception of the 6th and 12th month of life - although they decreased with age. This pattern was also seen in three out of 14 infants in a study by Einspieler and colleagues^[9]. Yet, while there was no association with excitement or crying in these three individuals, we occasionally observed this pattern in co-occurrence with possible signs of agitation such as stiff fisting and a stiff body posture. Furthermore, during the 5th week of life these tremulous movements were seen in each sequence in which the girl was manipulated. However, considering all data, they occurred more often when the participant was alone.

Stereotyped movements with the hands together - such as washing movements and repetitively putting both hands together followed by their immediate separation - were seen from 8 months onwards. These patterns have been reported by several other researchers and have been identified as characteristic stereotypies in RTT^[4,7,6,17,19]. Against our expectation that these typical stereotypic movements would increase over time, the highest rates of consistency were found at 8 months for repetitive hand-to-hand movements and at 9 months for washing movements. Afterwards both patterns decreased and were even absent during the 11th month of life.

Besides the consistent occurrence of abnormal hand behaviours, we also observed a variety of normal hand movements and postures. These were present throughout the whole observation period with high rates of consistency. We also revealed that the participant was able to achieve the most important milestones in the development of hand function at an adequate age. Reaching and grasping were observed for the first time at 3 months of age, object manipulation and object-to-mouth movements at 4 months, transfer of an object

from one hand to the other at 6 months, index finger pointing at 8 months and pincer grasps as well as differentiated bimanual hand movements at 10 months of age. These results were consistent with those of some other researchers who reported that the many infants were able to achieve these milestones before regression, although some of them with delay^[4,7,8,14,20,21].

Tough we focused on the observation of the hands, we occasionally noticed normal and abnormal patterns in other parts of the body. The gross motor development of the girl was seemingly normal as she displayed important milestones; most of them at an adequate age. She kept her head in midline from 7 weeks (2 months) onwards. Body weight support on the hands was seen for the first time at the beginning of the 5th month. At 8 months she could balance her weight on the hands and the knees and crawling was seen from the 9th month onwards. Also from 9 months onwards she was able to sit unaided. From the beginning of the 10th month onwards the girl pulled herself into standing with support of furniture. First steps with support were observed during the 12th month. Abnormal patterns especially concerned general body posture, arm postures and the head and face. During the first month of observation (2nd month of life) we saw asymmetric tonic neck postures during which the "occipital" hand was more active. This is different to normal developing infants, who preferentially perform movements with the hand they see^[22]. Earlier parental reports and retrospective video analysis often revealed that the patients were floppy or very placid during infancy^[11,15]. We observed very placid behaviour associated with slumped body posture during the 2nd to 5th month of life and again from the 10th to 12th month of life. Yet, our participant also displayed episodes of extreme postural stiffness, as did eleven out of 22 infants in a study by Einspieler and colleagues^[6]. Both features were especially seen at the beginning and at the end of the observation period. During mid-infancy, our participant showed an unusual posture during which she kept both arms and legs lifted and balanced her body weight on her trunk. This behaviour has so far never been reported by other researchers. Consistent with the findings of a case study by Temudo, we occasionally observed dystonic postures of the upper limb. Stereotypic movements apart from those of the hands occurred as repetitive head nodding, asymmetric eye opening and closing and tongue protrusion. All these features have also been found in several infants in a study by Einspieler and colleagues^[6].

Family videos have been used by several other researchers in order to study the early development of patients with RTT^[1,4-6,9]. They have become an important tool to identify

early behavioural and developmental deviations by direct observation before the disease becomes obvious during the regression period. Although it needs extensive observer training, this method is reliable due to its independence from parental recall and the possibility to perform repetitive frame-by-frame analysis^[23].

Our study is unique due to large extent of data and the continuity of the recordings. We were able to analyse video recordings with a total duration of 391 minutes (6 hours and 31 minutes) which showed at least one hand during each month from the 2th until the 12th month of life. Thus, we could almost continuously observe the development of hand function and identify the approximate time of onset of abnormal behaviours. Muting of the recordings avoided distraction by environmental noise.

Yet we have to admit that our analysis has certain limitations. First of all we cannot generalise our results as we performed a single case study. Furthermore, the sequences used for observation were of different length and the environmental situations (i.e. manipulation or interaction, objects provided, the girl alone) or the girl's posture (i.e. in supine or prone position, sitting, standing) sometimes changed within a sequence. Thus, our calculations might be biased and we were mostly unable to evaluate correlations between different situations or postures and the occurrence of certain patterns. We also might have failed to identify some behaviours if they were performed without being recorded. This lack of data also makes an exact determination of the time of onset of the different patterns and their accurate rates of consistency difficult. Still, we believe that our analysis provides reliable results which are very close to the actual development of the girl's hand movements and postures.

Summarising, we can say that abnormal hand patterns were present already in early infancy with subsequent occurrence during each month of the observation period. They furthermore showed an overall increment in variety and rates of consistency. Still, and against our expectation, normal hand behaviours were always predominant over abnormal patterns. Our findings might facilitate the search for early diagnostic methods of RTT and the understanding of the underlying CNS malfunction.

Further research needs to be done in order to evaluate our results in a larger cohort and to find possible correlations between different environmental factors and the occurrence of certain behaviours.

References for 4 Discussion

- [1] Kerr AM, Montague J, Stephenson JB. The hands, and the mind, pre- and post-regression, in Rett syndrome.

- Brain Dev 1987;9(5):487-90.
- [2] Engerström IW. Rett syndrome: the late infantile regression period-a retrospective analysis of 91 cases. *Acta Paediatr* 1992;81(2):167-72.
 - [3] Nomura Y, Segawa M. Clinical features of the early stage of the Rett syndrome. *Brain Dev* 1990;12(1):16-9.
 - [4] Marschik PB, Einspieler C, Oberle A, Laccone F, Prechtl HF. Case report: Retracing atypical development: a preserved speech variant of Rett syndrome. *J Autism Dev Disord* 2009;39(6):958-61.
 - [5] Burford B. Perturbations in the development of infants with Rett disorder and the implications for early diagnosis. *Brain Dev* 2005;27 Suppl 1:3-7.
 - [6] Einspieler C, Kerr AM, Prechtl HF. Is the early development of girls with Rett disorder really normal?. *Pediatr Res* 2005;57(5):696-700.
 - [7] Temudo T, Maciel P, Sequeiros J. Abnormal movements in Rett syndrome are present before the regression period: a case study. *Mov Disord* 2007;22(15):2284-7.
 - [8] Kerr AM. Early clinical signs in the Rett disorder. *Neuropediatrics* 1995;26(2):67-71.
 - [9] Einspieler C, Kerr AM, Prechtl HF. Abnormal general movements in girls with Rett disorder: the first four months of life. *Brain Dev* 2005;27 Suppl 1:8-13.
 - [10] Fehr S, Downs J, Bebbington A, Leonard H. Atypical presentations and specific genotypes are associated with a delay in diagnosis in females with Rett syndrome. *Am J Med Genet A* 2010;152A(10):2535-42.
 - [11] Kerr AM, Witt Engerström I. The clinical background of the Rett disorder. In: Kerr A, Witt Engerström I, editors. *Rett disorder and the developing brain*. Oxford: Oxford University Press; 2001. p.1-26.
 - [12] Leonard H, Moore H, Carey M, Fyfe S, Hall S, Robertson L, et al. Genotype and early development in Rett syndrome: The value of international data. *Brain Dev* 2005;27 Suppl 1:59-68.
 - [13] Marschik PB, Pini G, Bartl-Pokorny KD, Duckworth M, Gugatschka M, Vollmann R, et al. Early speech-language development in females with Rett syndrome: focusing on the preserved speech variant. *Dev Med Child Neurol* 2012;54(5):451-456.
 - [14] Segawa M. Early motor disturbances in Rett syndrome and its pathophysiological importance. *Brain Dev* 2005;27 Suppl 1:54-58.
 - [15] Leonard H, Moore H, Carey M, Fyfe S, Hall S, Robertson L, et al. Genotype and early development in Rett syndrome: The value of international data. *Brain Dev* 2005;27 Suppl 1:59-68.
 - [16] Huppke P, Held M, Laccone F, Hanefeld F. The spectrum of phenotypes in females with Rett syndrome. *Brain Dev* 2003;25:346-51.
 - [17] Temudo T, Oliveira P, Santos M, Dias K, Vieira J, Moreira A, et al. Stereotypies in Rett syndrome: analysis of 83 patients with and without detected MECP2 mutations. *Neurology* 2007;68(15):1183-7.
 - [18] Geerts WK, Einspieler C, Dibiasi J, Garzarolli B, Bos AF. Development of manipulative hand movements during the second year of life. *Early Hum Dev* 2003;75(1-2):91-103.
 - [19] Carter P, Downs J, Bebbington A, Williams S, Jacoby P, Kaufmann WE, et al. Stereotypical hand movements in 144 subjects with Rett syndrome from the population-based Australian database. *Mov Disord*. 2010 Feb 15;25(3):282-8.
 - [20] Hagberg B, Witt Engerström I. The Swedish series of females with Rett syndrome 1960-92. In: Hagberg B, editor. *Rett syndrome - clinical and biological aspects*. London: Mac Keith Press; 1993. p.21-26.
 - [21] Hagberg B.J. Rett syndrome: long-term clinical follow-up experiences over four decades. *Child Neurol* 2005;20(9):722-7.
 - [22] van der Meer AL, van der Weel FR, Lee DN. The functional significance of arm movements in neonates. *Science* 1995;267(5198):693-5.
 - [23] Marschik PB, Einspieler C. Methodological note: video analysis of the early development of Rett syndrome - one method for many disciplines. *Dev Neurorehabil* 2011;14(6):355-7.

4 Epilogue

4.1 Meeting the participant and her family

In summer 2012, after having finished data analysis, I had the extraordinary possibility to meet the study participant and her family. In this context I carried out a semi-structured interview with the parents focusing on the girl's early development. They kept meticulously recorded diaries about their daughter's development, about various group activities, and comments they had received from relatives and friends regarding their daughter. Information from medical examinations was available for 3.5 months, 7 months, 1 year, 2, 3 and 4 years of age.

Analysis of the data about somatic growth revealed that her head circumference (OFC) was between the 25th and the 50th percentile at 3.5 months but then declined and remained at or slightly below the 3rd percentile from 2 years of age onwards. Height already started to decrease from birth and was far below the 3rd percentile from 7 months onwards. Body weight was mostly between the 3rd and the 10th percentile except for 7 months and for 1 year of age when it was below the 3rd percentile.

For the first six month of life, the parents did not report any obvious developmental deviations. In fact, comparing to other infants in the mother-child gymnastic group the girl showed excellent skills and behaviours. The grandparents praised her gentleness and wondered about her extreme patience. At about 2 to 3 months of age the parents noticed that the girl's head was mainly turned to the right and she performed better with the right hand than with the left. By the end of the 3rd month, the parents perceived that during fisting she still kept her thumb enclosed by the other fingers. Furthermore, at 4 months she stiffened her legs when she was passively rolled from prone into supine during mother-child gymnastics. Concerning her vocal development she stopped cooing during the 4th month of life and started to “shriek” and “crow” instead. Two months later she babbled “bah-bah” for the first time.

During the second half of the 1st year the parents began to notice some peculiarities in their daughter's development. They reported that the girl was smaller and had less weight than others, which was confirmed by medical examinations at 7 month and at 1 year. They were concerned because she only recognised her father with some delay when meeting him in the street. Once, at 9 months the girl pitched headlong into the snow but did not show any sign of discomfort (i.e. she did not cry). Furthermore, from 10 months onwards she

sometimes crossed the long finger of the left hand over the index finger during crawling – a behaviour which we also identified in our video analysis (see chapter 2.2 Results and figure 2.29). Her motor development seemed to decelerate: Although she started to crawl at 8 months and could finger feed herself as well as drink from a beaker, she could not walk – neither with the parents' assistance nor without support - by the end of the first year. Walking with assistance was possible from 13 months onwards and walking free was delayed to 18 months of age. From 1 year of age onwards she increasingly lost her interest in toys and from 15 months onwards her fine motor skills started to deteriorate. Grasping and keeping an object in her hands or bringing it to the mouth became difficult. Furthermore, her speech development was limited to three words (“Mama”, “yes” and “no”) and even these three words were lost after the age of 18 months. According to her parents, she started to show first stereotyped movements at 21 months: She put her left hand to the mouth and twirled her hair with the right hand. If her arms were restrained and thus she could not put her hands into the mouth, she performed washing movements with the hands in her lap.

At this time (21 months of age), the parents consulted a paediatrician who referred them to a specialist. At 22 months of age the girl was clinically diagnosed with RTT and genetic testing at 2 years of age revealed a p.R168X mutation in *MECP2*.

4.2 The participant's current status

When we met, the participant of our study was 11 years and 5 months old. As expected, it took her some time to get used to my presence but by the end of the day she seemed to be quite familiar with me. During the day of my visit I was able to accompany and watch her during different activities such as feeding, going for a walk, watching animals or spending time with her 7-year-old sister. I very much appreciated the relationship between the girl and her little sister. Our study participant obviously enjoyed to watch her sister playing and laughed when her sister joked around and hugged her (Figure 4.1). Even though the play was sometimes boisterous, and once her little sister splashed water into her face, she never showed any signs of discomfort and it was the parents who had to intervene.



Figure 4.1: The girl laughing while being hugged by her little sister. With permission from the participant's parents.

At the time I met her, she showed constant hand stereotypies and had hardly any purposeful hand function. Stereotypies were mostly performed as mouthing of the right hand while the left hand enclosed and kneaded the right hand (Figure 4.2). Occasionally, she also showed washing movements with the hands on chest level or in her lap. Her purposeful hand function was limited to pressing the button of her device of alternative communication. She was unable to speak, yet could communicate with her parents with her eyes. Her mother told me that she could demonstrate agreement by closing her eyes. The parents further reported that they training their daughter's communication abilities by using symbolic cards and the girl could express herself by putting her face close to a card. She also had a device of alternative communication, which could record comments of her parents or teachers and by pressing its button the girl could listen to these recordings. I had the chance to watch her handle this tool and she obviously enjoyed it.



Figure 4.2: The participant performing hand stereotypies. The right hand is put into the mouth while the left hand is kneading the right hand. With permission from the participant's parents.

Although her body posture was quite stiff, she had no severe ambulation difficulties and walking seemed to be easy especially when driven by inner urge (e.g. when she wanted to get close to her sister). Her somatic features – both weight and height - were below the 3rd percentile and her body mass index was 15.87. She had a very slight right-convex scoliosis and wore ankle-foot orthoses in order to prevent the progress of a pes equinus . According to her parents, breathing abnormalities such as breath holding and hyperventilation were occasionally present; hyperventilation especially occurred when the girl was agitated. The parents also reported that she was teeth grinding from time to time. She had developed epileptic seizures at 4 years of age and had been taken antiepileptic medication ever since. She had been seizure free for one year yet restarted to show prognostic symptoms such as absences co-occurring with a slumped body posture and tremulous movements of the whole body 2 months before my visit.

Asking her parents about her current favourite activities revealed that she loved music; listening to her favourite songs could calm her when she was agitated. She furthermore liked horseback riding, dancing, cuddling, watching pictures and being in company. During the last three years she had improved her communication skills, had become more interested in her surroundings, more patient and able to concentrate longer and had improved her ability to show her feelings.



Figure 4.3: Hand-stereotypies cease and the participant laughs while watching the water running in the water trough (in front of her). With permission from the participant's parents.

4.3 My personal experience with RTT and with this thesis

The first time I heard about RTT was in 2007. During a two-week holiday for children and adults with cognitive impairments and physical handicaps, organised by an Austrian NGO, I was responsible for the care of a 13-year-old girl with RTT. Initially I was shocked by her severe impairment and overcharged as she could not communicate her needs in the usual way. Yet, these two weeks turned out to be a wonderful experience for me. Spending time with that girl, watching her smile when I was singing to her and learning to “read” her expressions aroused my interest in this disorder. I maintained contact with the family of that girl and over the years I met other girls with RTT. Soon I decided to look for a possibility to write my thesis about RTT and I was privileged to find my two supervisors Prof. Christa Einspieler and Ass.-Prof. Peter Marschik who have performed extensive research on the early development of patients with RTT. They offered me to carry out a case study about the development of hand function and stereotypies using the unique extensive video material this particular family had generously provided for research. Working with them was a great experience. From the beginning I felt welcome in their office and enjoyed every day I spent there during the video analysis. Besides their continuous readiness to help me with the analysis I could also always count on them when I needed information for the theoretical part of this work. They repetitively corrected my writing and were very patient – despite my insufficient language skills. I can for sure say that they are both an extraordinary model of how a perfect supervisor should be.

I was amazed at the extensive data provided by the parents of our study participant. They apparently wanted to create a video diary for their daughter – unaware that these videos would one day be an important resource for research. I honestly thank the parents of our participant to have shared these videos with us. By doing so they have opened their home to us and let us be part of their private life.

Due to my previous lack of experience with infants, I first had some difficulties to distinguish between normal and abnormal behaviours in the beginning. Yet, I always obtained assistance from my supervisor who was ready to analyse a number of sequences together with me. It was very interesting when comparing our findings to those of other studies because several features were similar. For me, the most striking pattern was the repetitive opening and closing of the hand which the girl performed excessively when she was seemingly stressed or agitated.

One of the “highlights” during working on my thesis was meeting our participant and her

family. I felt heartily welcomed and we spent a wonderful day in the Austrian Alps. It was moving to see how this girl I had so often seen on the screen, had developed. I also enjoyed meeting her little sister – a cheerful girl who obviously and cordially loves her older sister. I am convinced that especially this sister is such an enrichment for our study participant and helps her more than any kind of therapy would ever do. It was also a special moment having the possibility to share our results with the girl's parents and talk about their memories and their records of the early development of their daughter.