Rett Syndrome

Citation for published version (APA):

Townend, G. S. (2019). *Rett Syndrome: recognising the communication challenges, needs and potential of individuals living with a rare disease*. [Doctoral Thesis, Maastricht University]. ProefschriftMaken Maastricht. <https://doi.org/10.26481/dis.20190704gt>

Document status and date:

Published: 01/01/2019

DOI:

[10.26481/dis.20190704gt](https://doi.org/10.26481/dis.20190704gt)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Rett Syndrome:
Recognising the Communication Challenges,
Needs and Potential of Individuals
Living with a Rare Disease

The research presented in this thesis was conducted at the Governor Kremers Centre (GKC) – Rett Expertise Centre Netherlands-GKC and at the Departments of Paediatrics and Otorhinolaryngology, Maastricht University Medical Centre, the Netherlands.

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ISBN 978-94-6380-395-3

Cover design by Lottie Townend (adapted from an original artwork of her own entitled "Together")

Printed by ProefschriftMaken || proefschriftmaken.nl

**Rett Syndrome:
Recognising the Communication Challenges,
Needs and Potential of Individuals
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DISSERTATION

to obtain the degree of Doctor at Maastricht University,
on the authority of the Rector Magnificus, Prof. dr. Rianne M. Letschert,
in accordance with the decision of the Board of Deans,
to be defended in public on Thursday 4 July 2019, at 16.00 hours

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Chapter 1

General Introduction and Outline of the Thesis

General Introduction

Aim of the Thesis

Rett syndrome is a complex, multifactorial rare disease that is estimated to affect approximately one in 10,000-12,000 females [1-4] and, much more rarely, males [5-8]. Diagnosis is made according to clinical criteria, revised by Neul et al. in 2010 [9], which may be confirmed by genetic analysis. “Necessary” criteria are defined as a period of regression followed by recovery or stabilisation accompanied by four “main” or core criteria. These are: “complete or partial loss of acquired purposeful hand skills, complete or partial loss of acquired spoken language, gait abnormalities and stereotypic hand movements” [9]. One of the “supportive” criteria is recognition of “intense eye communication – eye pointing” [9, p. 946]. The loss of spoken language and other communication challenges have a profound impact on the lives of individuals with Rett syndrome and their families. According to a ‘Severity of Symptoms Survey for People with Rett Disorders’ conducted by the Rett Disorders Alliance UK in 2016, parents rated ‘communication issues’ as having the single biggest impact on quality of life both for individuals with Rett syndrome and for their parents and other family members¹.

This thesis presents Rett syndrome as a rare disease, with a particular focus on applied research conducted by the Rett Expertise Centre Netherlands-Governor Kremers Centre (GKC), a single rare disease-focused Centre of Expertise. The applied research explores a number of elements relating to the communication challenges, the communication support needs and communication potential associated with Rett syndrome, in order to increase knowledge and understanding of those aspects of the disease, their impacts on daily and family life, and the supports and interventions required to maximise communication and improve quality of life for individuals and families living with Rett syndrome.

Following a short introduction to Rett syndrome, its genetics and main phenotypic features, this first chapter sets Rett syndrome in the context of rare diseases, rare disease policy and rare disease initiatives in Europe. It then places communication skills and impairments in communication into the framework of the World Health Organization’s (WHO) International Classification of Functioning, Disability and Health before outlining the structure of the rest of the thesis, and introducing the applied research aims addressed in the papers presented in the main body of the thesis.

¹ The survey was distributed online and completed by 156 parents of individuals of all ages with Rett-related disorders. It included questions relating to 79 symptoms or problems under ten main headings of breathing, seizures, communication, bone strength and muscle tone, mobility, hands, eating and nutrition, bowel and gut problems, sleeping, anxiety, and a final category of ‘other’. The results of the survey were presented at a meeting of the Rett Disorders Alliance UK Working Group, London, 3rd November 2016.

Introduction to Rett Syndrome

Since the first descriptions by Dr. Andreas Rett in 1966 [10, 11] and Dr. Bengt Hagberg in 1983 [12] of a cluster of symptoms that were to become known as Rett syndrome, and the identification in 1999 of a causative mutation in the Methyl-CpG-binding protein 2 (*MECP2*) gene [13], around 800-900 different *MECP2* mutations have been identified [14, 15]. Over half of these are considered to be pathogenic. In addition, a further 69 genes have recently been discovered that may contribute to a Rett-like presentation [14]. Rett syndrome is life-long and life-limiting, with stagnation and regression of skills typically occurring between 6-18 months of age in cases of classic Rett syndrome; the onset is somewhat later for individuals with atypical Rett syndrome, for example, the preserved speech variant (PSV) [9, 16-18]. There is increasing awareness that the period prior to regression may also be more affected than previously thought [16, 19-22].

Rett syndrome affects multiple body systems, due to the role of *MECP2* as a transcriptional regulator [23-25] expressed mainly, but not only, in neurons [26]. *MECP2* influences many different biological pathways on numerous levels [23]. As outlined above, individuals affected by Rett syndrome must contend with a loss of acquired skills, notably, loss of spoken language and fine motor skills/purposeful hand use, further exacerbated by stereotypical hand wringing/clasping/mouthing and gait abnormalities [9]. In addition, many experience further symptoms and co-morbidities, to differing degrees of severity, such as disturbances in muscle movement and tone (dystonia, dyspraxia, ataxia), breathing irregularities, impaired sleep, scoliosis/kyphosis, gastro-intestinal problems, disruptions in sensory regulation, and seizures that may or may not be epileptic in origin [27-31]. With appropriate management of symptoms, however, individuals with Rett syndrome can live into adulthood [32-36], and can demonstrate an ability to learn and regain or develop new skills given appropriate support and intervention once the early stages of stagnation and regression are passed [37-41].

Within the vast array of possible mutations there are eight most common *MECP2* hotspot mutations, which account for around half of all mutations identified in individuals with classic Rett syndrome. Different mutations generally appear to confer different degrees of symptomatology [42, 43], yet individuals with the same mutation can also present with differing symptoms and very different degrees of severity [44, 45]. X-inactivation, variable distribution of normal and mutant X chromosomes within the brain, an individual's genetic background, and environmental influences all play a major role in the gene expression [14, 46-49]. Ambulation, hand use and age at onset of stereotypies are also reported to be strongly linked to overall disease severity [50]. Thus, receiving a diagnosis, even one accompanied by confirmation of a specific genetic mutation, does not imply an identical life course for all individuals. One (or some) of the questions about their child may be answered for a family at the point of diagnosis but new questions continue to arise throughout life as new aspects, and new stages, of this rare disease are encountered.

The loss of language skills required in order to fulfil the core criteria is based on the loss of “best acquired spoken language skill, not strictly on the acquisition of distinct words or higher language skills” [9, p. 946]. There is variation between individuals. Thus, some individuals with Rett syndrome may only babble prior to regression while others may learn to use a number of words or phrases, that are then lost; some individuals will retain those words and/or phrases post-regression and may add to them; some will never develop spoken language at all [16, 17, 30, 51-54]. There is a lack of clarity regarding the receptive language (and cognitive) levels that may be ascribed to individuals with Rett syndrome, with much literature suggesting it is characterised by severe intellectual impairment [e.g. 15, 55-57]. In contrast, however, there is much anecdotal evidence and, increasingly, newer studies that suggest this is not necessarily so, and that some individuals with Rett syndrome are able to demonstrate receptive language and levels of cognition on a par with their neuro-typical peers if their physical and spoken language deficits are accommodated, for example, by adapting assessments for eye gaze [58, 59]. Almost all individuals with Rett syndrome benefit from the use of alternative and augmentative communication (AAC) strategies and techniques (both low tech.² and high tech.³ systems), in particular those accessed via eye gaze [39, 52, 60-62].

Rett Syndrome as a Rare Disease

With a reported incidence of 1 in 10,000-12,000 females, Rett syndrome is classified as a rare disease for good reason. At the present time, around 7,000 rare diseases have been identified, affecting some 300-350 million people globally [63]. However, the exact number is difficult to quantify as definitions of ‘rare disease’ vary. In Europe a disease is said to be rare if it affects fewer than 1 in 2,000 people and in the US, according to the US Rare Diseases Act of 2002, if it affects fewer than 200,000 Americans at any one time [64]. Around 30 million people are estimated to be living with a rare disease in the European Union (6-8% of the population) [65] and 25-30 million in the US [66]; approximately 80% of rare diseases are genetic in origin [67].

According to the NGO Committee for Rare Diseases⁴, the challenges for people living with rare disease can be attributed to the following factors:

- “Patients and experts are few and geographically scattered
- Little information about the diseases, knowledge and good practices are limited

² Low-tech AAC = a system that is not electronic and does not require a power source e.g. individual objects, photos, communication board/ book.

³ High-tech AAC = an electronic device with speech output. The screen can have a static or a dynamic display and the output can be recorded/digitized speech or synthesized-speech. High-tech systems range from single message devices to complex computer-based systems.

⁴ The NGO Committee for Rare Diseases (United Nations, New York) is a substantive committee established under the umbrella of the Conference of NGOs in Consultative Relationship with the United Nations. It was initiated by the Ågrenska Foundation and EURORDIS to bring increased political recognition to the challenges of rare diseases globally. It’s inaugural meeting was held in New York in November 2016.

- Little and fragmented scientific research as funding and resources are scarce
- Slow, or often inaccurate diagnosis
- Isolation: for patients, families, their health and social care professionals, their researchers
- Only 5% of rare diseases, have adequate treatments” [67].

Furthermore, the Committee states that, “The combined rare, complex and disabling nature of most rare diseases leads to serious unmet health and social needs for people living with rare diseases and their families’ well-being, autonomy and fundamental human rights” [67].

Doctors in general practice, therapists and other healthcare, education and social services professionals might only ever meet one person with Rett syndrome during their career or their lifetime. Indeed, many never encounter Rett syndrome. How can we ensure that professionals have the knowledge required, in anticipation of that one person they might meet, in order to assess and diagnose, to advise, intervene, and manage that individual’s needs? How can we ensure that affected individuals and their families find their way to those doctors, therapists, teachers who are knowledgeable and have the specialist skills they require? How can we ensure that individuals and families are given the support, help and resources they need at each stage of life’s journey? There are countries where at least a basic level of health care is accessible free at the point of use (funded through insurance or taxation), countries where children with disabilities generally have access to therapies and to (special needs) education, countries where individuals and families can access specialists with knowledge of their particular disease or syndrome, and can access appropriate or at least adequate support, resources, and funding. But there is variability in and between countries; there is still inequality in provision and there are gaps in specialist services, in knowledge, funding, resources, support. There are people who live in countries with no immediate access to any of these things, where children with disabilities have no right to education, where therapy and other healthcare and social services are scarce. How can we ensure provision for them? How can we ensure provision for families who are economically more disadvantaged, families whose child has more severe needs? How can we ensure that these needs are met in different jurisdictions with different political and economic backgrounds and different realities of access to health care? Centres of Expertise have an important role to play in all of these contexts [68].

The World Health Organization and European Union Position on Rare Diseases

Recognition of the needs of people with rare diseases, including Rett syndrome, has grown in the political sphere in recent years. According to a recent address given by Dr. Rüdiger Krech (Director of Universal Health Coverage and Health Systems, World Health Organization) to the European Conference on Rare Diseases in Vienna in May 2018, “rare

diseases represent a major challenge in public health that has been largely ignored. Consequently, this is a field in public health and research that would certainly benefit from globally concerted action and international collaboration.” [63 p.1]. In representing the WHO position on rare diseases, Dr. Krech further recommends that, while treading a cautious path towards a ‘cure’ for some rare diseases, ‘pooling’ of expertise, data, research and development, ‘collaboration’ to establish international best practices and set standards for diagnosis, care and treatment, and ‘smart innovation’, particularly in relation to gene editing, should all be developed further and put into practice [63, pp. 2-3].

Within Europe, the Council of the European Union (EU) recommended in 2009 that all Member States develop national action plans for rare diseases by 2013 (Council Recommendation of 8 June 2009 on an action in the field of rare disease (2009/C 151/02)) with the ultimate goal being to “guarantee that individuals affected by rare disease have access to timely and adequate medical and social care” [69]. This was followed in 2011 by Directive 2011/24/EU on the Application of Patients’ Rights in Cross-Border Healthcare which, amongst other things, set out provisions for the creation of European Reference Networks (ERNs) and an obligation on Member States to identify national Centres of Expertise for Rare Diseases to feed into the ERNs. The Rett Expertise Centre Netherlands-GKC is an example of a national, single rare disease-focused Centre of Expertise realised in accordance with the EU policy on rare diseases.

The Dutch Position on Rare Diseases in General and Rett Syndrome in Particular

In response to the 2009 EU Recommendation, the Dutch National Plan for Rare Diseases was approved by the Minister of Health and adopted in the Netherlands in November 2013. At the present time there are 350 nationally recognized and government-endorsed Centres of Expertise in the Netherlands. These were created according to the criteria specified by EUCERD⁵ [68] and collectively cater for a broad spectrum of rare diseases [70]. The majority of these Centres are affiliated with the eight University Medical Centres in the Netherlands. The Expertise Centre for Rare Syndromes and Cognitive Disorders at Maastricht University Medical Centre (MUMC+) includes the Rett Expertise Centre Netherlands-GKC in its remit. The Rett Expertise Centre was opened at MUMC+ in 2011, as an initiative of the Governor Kremers Centre with support from the Dutch Rett parents’ organisations (Stichting Terre – Rett Syndroom Fonds and Nederlandse Rett Syndroom Vereniging (NRSV), the Dutch Rett Syndrome Association) and officially endorsed by the Dutch government as the national Centre of Expertise for Rett Syndrome. The Rett Expertise Centre Netherlands-GKC is multi-disciplinary in nature, combining patient care with basic and applied research. The patient

⁵ EUCERD was the European Union Committee of Experts on Rare Diseases; it was replaced in 2014 by the EC Expert Group on Rare Diseases.

care team, situated within the Department of Paediatrics of MUMC+, is responsible for, amongst other things, assessment and diagnosis, intervention planning, and provision of second opinions; the team liaises with locally-treating doctors and therapists. It offers a regular outpatient clinic and in-patient facilities. The research team, located within the Governor Kremers Centre of Maastricht University, focuses on (i) basic research relating to molecular analysis and biological pathways, including human cell lines research, (ii) applied research, primarily in paramedical and neurohabilitation fields, for example, relating to the physical and communication challenges experienced by individuals with Rett syndrome.

Communication Skills and the International Classification of Functioning, Disability and Health

Being able to communicate allows an individual to express their needs and wants, their feelings and opinions, to make choices, build relationships, develop autonomy and independence, access education and participate in society. Difficulties in communication have a profound impact on quality of life. The loss of, or reduction in, ability to communicate in a conventionally-recognised manner (for example, by speech or hand signs) is one of the great challenges experienced by individuals with Rett syndrome [30, 42, 52, 71-73].

Underpinning successful communication is a complex matrix of requirements, both internal and external to an individual. Internal factors include their levels of arousal and alertness, their visual attention, visual perception, visual acuity, visual memory, oculomotor function, motivation and desire to communicate, awareness of cause-effect and reciprocity, understanding of the world around, and receptive language (language comprehension). External factors relate to the social, physical, geographical, cultural and political environments, for example, the people around an individual, their attitudes and actions, the supports, services, funding, resources and equipment offered. All of these can usefully be mapped onto the framework offered by the International Classification of Functioning, Disability and Health (ICF)⁶ [74], a framework that “conceptualises functioning as a ‘dynamic interaction between a person’s health condition, environmental factors and personal factors’” [75, p.5] (last updated 2018 [76]). Part One of the ICF framework considers functioning and disability according to two components: body functions and structures; and, activities and participation. Part Two explores contextual factors that are sub-divided into environmental and personal factors. According to the ICF there is a complex and dynamic (two-way) relationship between an individual’s health condition and the contexts in which they find themselves.

Difficulties in communication – whether due to impairments in body structures and functions or environmental and personal factors or any combination of those – pose the

⁶ The ICF was officially endorsed by all 191 WHO Member States in May 2001 (resolution WHA 54.21).

greatest barrier to individual autonomy and the freedom to make one's own choices, and to full and effective participation and inclusion in society. If we recognise the principles of the UN Convention on the Rights of Persons with Disabilities⁷ [77] then we have an obligation to work towards the reduction and, where possible, removal of those barriers. One of the responsibilities of an Expertise Centre is to consider people living with a rare disease in a holistic way, both at an individual level and at a group level. The ICF brings together medical and social models of disability [74 p.20]. It offers a common language for multi- and interdisciplinary working, and provides a framework onto which the diverse elements of basic and applied research and patient care (diagnosis, assessment, intervention, long-term management) can be mapped to form a coherent whole. The ICF and ICF-CY⁸ have also been suggested to be of particular value when applied to assessment and setting of intervention targets for adults and children with communication impairments and/or AAC needs [78-80]. The applied research presented in this thesis focuses primarily on three research aims, which together relate to three components of the ICF: body functions and structures; activities and participation; and, environmental factors.

Outline and Structure of the Thesis

The thesis is divided into two parts. The first part *"Setting the Context – Rett Syndrome as a Rare Disease"* (**Chapters Two – Four**) places Rett syndrome, and the Rett Expertise Centre Netherlands-GKC, within the context of rare diseases and rare disease initiatives. The second part *"Applied Research Relating to the Communication Challenges, Needs and Potential of Individuals with Rett Syndrome"* (**Chapters Five – Ten**) presents applied research conducted at the Rett Expertise Centre Netherlands-GKC, applied research that explores clinical, or symptomatic, aspects of Rett syndrome in greater depth, in this case research relating to the communication challenges, needs and possibilities of Rett syndrome.

Part One: Setting the Context – Rett Syndrome as a Rare Disease

Chapters Two and Three describe rare disease policy and the provision of services in Europe. **Chapter Four** focuses on available databases containing genetic and phenotypic information on Rett syndrome.

⁷ The Convention and its Optional Protocol (A/RES/61/106) was adopted at the United Nations Headquarters in New York in December 2006. It was opened for signature in March 2007 and entered into force in May 2008.

⁸ The ICF-CY is a "derived" classification of the ICF for Children and Youth. It was decided in 2012 to merge the ICF and ICF-CY so that the ICF-CY would remain a special derived classification but as a "linearization" of the common ICF foundation.

Chapter Two

This is a short communication that asks what the European Union policy on rare diseases is; it provides a synthesis of recent developments and considers the implications for Rett syndrome.

Chapter Three

This chapter asks how far EU rare disease policy is being translated into practice, for individuals with Rett syndrome in particular. It provides a country by country comparison of factors such as: the identification of experts in Rett syndrome and creation of expertise centres, existence and use of rare disease databases for cataloguing and sharing data on Rett syndrome, and the contribution made by national Rett syndrome associations and foundations. It identifies parents' wishes and aims for the future and suggests models of good practice for fostering collaborations that will strengthen existing services, facilitate diagnosis, advice and support.

Chapter Four

This explores initiatives (within the EU and beyond) to share data in order to deepen knowledge and understanding between researchers and clinicians. It focuses on an exploratory study of 13 genotype-phenotype databases, using Rett syndrome as a test case and employing a search for five *MECP2* mutations in order to evaluate the functionality of each database. The paper identifies the positive aspects as well as the current shortcomings of the databases and suggests future developments that would improve the strength and value of the databases.

Part Two: Applied Research Relating to the Communication Challenges, Needs and Potential of Individuals with Rett Syndrome

Chapter Five introduces the second part of the thesis by setting the scene for the applied communication research chapters that follow. **Chapters Six – Ten** address three applied research aims, namely: (1) to increase knowledge and understanding of aspects of Rett syndrome including early development of communication skills and features underlying communication (**Chapters Six – Eight**); (2) to investigate the impact of communication needs on daily/family life and the supports required to maximise development of communication (**Chapter Nine**); and, (3) to develop guidelines for assessment, intervention and long-term management of communication that will benefit individuals with Rett syndrome, their families and professionals working with them, and that contribute to international sharing of good practice (**Chapter Ten**).

Chapter Five

This chapter provides a state-of-the-art overview of communication, cognition and behaviour in individuals with Rett syndrome.

Chapter Six

This presents research that seeks to extend understanding of Rett syndrome by identifying pre-diagnostic indicators, with a focus on early communication skills. It compares response to name as an early marker of social reciprocity in 10 infants with classic Rett syndrome and five with atypical (PSV) Rett syndrome, through means of retrospective video analysis.

Chapter Seven

One of the essential pre-requisites underlying use of eye gaze for communication is an intact oculomotor system. This chapter reports on the first part of a two-part exploratory study to assess oculomotor movements (saccades, smooth pursuit, optokinetic nystagmus and vestibulo-ocular reflex) in 18 individuals with Rett syndrome using electro-nystagmography (ENG). Their results are compared with those of 16 typically developing children.

Chapter Eight

In this chapter, the second part of the two-part oculomotor study is reported. This explores in greater detail the difficulties encountered when using regular ENG testing with individuals with Rett syndrome. It analyses the responses of 17 individuals with Rett syndrome according to two factors: attention and quality of electrode signals, and compares the results with those of 16 typically developing peers.

Chapter Nine

This reports on a qualitative study conducted with parents of children and adults with Rett syndrome living in the Netherlands. It presents the results of an online survey completed by 63 families, with regard to their experiences of eye gaze technology as a form of AAC. It evaluates the advice, training and support they receive in relation to this, includes measures of progress in the development of the child's communication skills, and ratings of parental satisfaction with both the technology and the support. (It should be noted that this paper was written before the research in **Chapters Seven and Eight** was undertaken and, in part, advocates that work. However, the paper presented in **Chapter Nine** appears here as it addresses the second applied research aim.)

Chapter Ten

The final research chapter in **Part Two** focuses on the development of international guidelines for the assessment, intervention and long-term management of communication in individuals with Rett syndrome. This combines available evidence (systematic reviews of literature) and lived experience (surveys conducted with a broad group of parents and communication professionals across multiple countries) with expert consensus. In particular, the chapter presents the results of the two-stage modified Delphi process that followed the extraction of statements and recommendations from the systematic literature reviews and surveys, leading to the formulation of the end product, the guidelines.

Advances in knowledge and understanding, together with gaps and challenges, and avenues for further research and development in the field of communication and Rett syndrome are identified, within each chapter and in the general discussion (**Chapter Eleven**) at the end of the thesis. The final chapter (**Chapter Eleven**) also reflects on the societal relevance of the applied research topics, especially on the importance of parent and professional collaboration in improving quality of life for individuals living with a rare disease such as Rett syndrome.

Please note:

1. UK English spelling is used throughout this thesis except where a paper was published in a journal requiring US English spelling. In that case, the thesis chapter reflects the spelling of the journal.
2. In most cases throughout the thesis the gender-neutral term “individuals with Rett syndrome” or “people with Rett syndrome” is used in recognition of the fact that, although rare, boys and men can be diagnosed with Rett syndrome too. Occasionally, there may be references to “girls” or “women with Rett syndrome” or to parental reports of their “daughter(s)” rather than “child(ren)”; these should also be read as referring to anyone with Rett syndrome.
3. According to accepted scientific convention, the term “Rett syndrome” is shortened to the abbreviation “RTT” in all of the published papers included in this thesis, except for **Chapter Ten**, which is in line with the specifications of that particular journal. Outside of the published papers, the rest of this thesis uses “Rett syndrome” in full.

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Part One

Setting the Context:
Rett Syndrome as a Rare Disease

Chapter 2

Rett Syndrome as a Rare Disease: a European Perspective

Published as:

Townend, G.S., van Kranen, H.J., van der Stel, R., van den Berg, M., Smeets, E., van Waardenburg, D., & Curfs, L.M.G. (2015). Rett Syndrome as a Rare Disease: a European Perspective. *Public Health Genomics*, 18(4), 233-236. doi:10.1159/000381139.

Rett Syndrome

Rett syndrome (RTT) is a rare neurodevelopmental disorder, which predominantly affects females. It results from a genetic mutation on the X chromosome, several forms of which have been identified, the most common occurring in the *MECP2* gene. Severity varies according to the specific mutation. The syndrome is typically characterised by seemingly normal development in the first months of life followed by a regression in skills which begins between 6 and 18 months of age. Individuals with RTT demonstrate a loss of motor and communication skills; they may develop severe breathing abnormalities, epilepsy and scoliosis. It is a severe, lifelong disorder, generally resulting in a shortened life expectancy.

Diagnostic Process

Rapid advances in DNA analysis, especially in ‘next generation sequencing’ technology are significantly improving the diagnosis of rare Mendelian disorders, including those underlying various forms of severe intellectual disability (ID) [1, 2]. At present, over 500 genes are linked to ID, but these are likely to represent < 50% of all genes involved. For this reason, several research groups have applied family-based diagnostic exome and, more recently, genome sequencing as an unbiased diagnostic approach for individuals with severe, unexplained ID. Their results confirm the hypothesis that ‘de novo’ mutations are the most important cause of severe ID. De novo mutations have also been reported to play an important role in related disorders such as autism, epilepsy and schizophrenia [3].

In less than 10 years, the advantages offered by such advances in diagnostic techniques and knowledge have become clear. Shifting from array-based comparative genomic hybridization (array CGH) to whole genome sequencing (WGS) was shown in 2014 by Gilissen et al. [2] to increase the diagnostic yield for individuals with severe ID, especially if used as a first-tier test. This is beneficial to the detection and, ultimately, treatment of so-called rare disorders, including RTT (Fig. 1).

In the majority of individuals with RTT, mutations in the X-linked *MECP2* gene have been identified as the likely cause. Yet, even for the analysis of the *MECP2* gene, WGS may still offer advantages. In one individual, Gilissen et al. [2] identified a de novo CNV (Copy Number Variation; an intra-exonic deletion) in exon 4 of the *MECP2* gene. This deletion had not been detected previously even though a clinical suspicion of RTT had indicated both Sanger sequencing and MLPA (Multiplex Ligation-dependent Probe Amplification) screening, both of which proved negative in this case. This observation in a single individual confirms the power of WGS. Alongside the promise of potential benefit, however, the clinical implementation of genomic sequencing opens up a whole debate about how to interpret causality of (rare) sequence variants, how to act upon ‘incidental findings’ and how to share results among researchers and clinicians as well as how to communicate these findings to the affected individuals and their families.

Figure 1. Diagnostic yield for patients with severe ID (IQ < 50), specified by technology: genomic microarrays, WES (whole exome sequencing) and WGS.

Percentages indicate the patients in whom a conclusive cause was identified using the specified technique. Brackets indicate the group of patients in whom no genetic cause was identified and whose DNA was subsequently analysed using the next technology. Reprinted with the permission of Nature.

Rare Disease European Reference Networks and Centres of Expertise

In addition to genetic or molecular advances in recent years, there have been a number of important developments in Europe in relation to rare disorders. The 2005 Report of the High Level Group on Health Services and Medical Care [4] was fundamental in introducing the concepts of cross-border healthcare and of European networks of centres of reference, both of which have special relevance to rare disorders. Since then, these ideas have been further developed through the work of the European Commission's Rare Diseases Task Force (RDTF) and the European Union Committee of Experts on Rare Diseases (EUCERD).

In 2011, provisions for the development of 'European reference networks' (ERNs) were written into Article 12 of the Cross-Border Healthcare Directive (Directive 2011/24/EU) [5], where a specific reference is made to rare diseases. Article 13 also refers to the important relationship between ERNs, rare diseases, and the availability of treatment across borders. Integral to the concept of ERNs is the intention that national, multidisciplinary 'centres of expertise for rare diseases' (CEs for RD) will be identified by Member States (MS) and their knowledge and expertise shared within the structure of ERNs. Quality criteria for such CEs were also specified by EUCERD in 2011 [6]. Both the European dimension of CEs and their function as 'key elements of the future ERNs' is stressed (p.8).

More recently, in 2013, recommendations for Rare Disease ERNs (RD ERNs) were set out in greater detail by EUCERD [7]. RD ERNs are described as providing the 'framework for healthcare pathways for RD patients through a high level of integrated expertise' (p.5) with nationally designated CEs as the 'core participants' (p.5) working in 'collaboration with healthcare providers, laboratories, patients and individual experts within Member States and between Member States' (p.2). The integral role of patient organisations is recognised in this. Despite the need for flexible structuring to accommodate differences between

national healthcare systems and medical areas, certain core elements are prescribed. These include: the creation and use of disease registries; the development and sharing of good practice guidelines and common training and education tools; and the use of tele-expertise. Ultimately, it is suggested, patients will benefit from improvements in diagnosis, care and knowledge and the development of new therapies that can be facilitated through such exchange.

In order to add further substance to these recommendations, EUCERD also published recommendations for core indicators for national plans/strategies in relation to rare disease in 2013 [8] as well as recommendations specific to RD patient registration and data collection [9]. The core indicators elaborate upon the Council of the European Union's 2009 recommendations¹ that MS develop their own action plans for rare diseases. Amongst other things, these recommendations support the requirement for MS to create (or support existing) CE for RDs, to participate in RD ERNs, to develop good practice guidelines for RDs and to build RD registries. The patient registration recommendations provide explicit detail for MS on this latter topic.

In October 2014, EUCERD held a joint action workshop on the topic of RD ERNs and structural funding. The focus of the workshop was to review progress in MS to date. During the workshop, the heterogeneity of existing CEs and networks was addressed, and the idea of grouping RDs for future ERNs was agreed. In total, 25 clinical disease 'areas' were identified as a strategic starting point with one RD ERN per area, offering the 'concept of an EU system for RD ERNs within which all patients could find a home' [10] (p. 6). In this way, it was envisaged that variations between countries in size, population and medical models/approaches to RDs could be overcome.

European Rett Expertise Centres and Databases

In order for the RD ERNs to move from a paper-based concept to a working reality, and in preparation for the official call for ERNs expected in December 2015, it is important that CEs are established across Europe. The Rett Expertise Centre, Maastricht University Medical Centre, is one example of a recently-formed single-focus CE, hosted within the Governor Kremers Centre which researches into other rare diseases such as Prader-Willi syndrome and Angelman syndrome. Based at the academic hospital and the University of Maastricht, the Rett Expertise Centre brings together specialists in fields such as genetics, (child) neurology, paediatrics, endocrinology, communication, and orthopaedics. It has a particular interest in brainstem neurophysiology and offers inpatient facilities for, amongst others, orthopaedic surgery and cortico-bulbar assessment.

¹ Council Recommendation of 8 June, 2009, on an action in the field of rare diseases (2009/C 151/02).

The Rett Expertise Centre Maastricht is a founding member of ESRR, the European Scientific Rett Research Association [11], a collaborative European platform for research focussing on RTT.

At the time of writing, and according to information first shared by Rett parent associations during the third European Rett Syndrome Conference held in Maastricht in October 2013 (ERSCM 2013) [12], between five and ten European countries benefit to varying degrees from the services of a national Rett Expertise Centre or from specialised multidisciplinary Rett Clinics, some of which are housed within centres for rare diseases. Several European countries have one or more hospitals that can provide a diagnostic service, with one or two medical experts able to offer advice and clinical management specific to RTT. Other European countries have services for general disabilities, but no-one specialised in RTT (for recent information on selected countries, see [13]. In these cases, the role of the national parent association, where one exists, is crucial in helping to raise awareness, disseminating information and knowledge, providing support for families and professionals and lobbying for change.

A number of European countries have some form of national database or registry for RTT, and/or may contribute to a larger European or international database such as InterRett or the Rett Networked Database. As of 2014, the Rett Networked Database contained information on just over 2,000 patients from 14 countries across Europe and further afield [14].

Implications for Rett Syndrome of the European Policy on Rare Diseases

At the close of ERSCM 2013 in October 2013, the organising committee and *Rett Syndrome Europe* signed a joint statement declaring their support for the European Union policy on rare disorders and defining more precisely the wishes of the European parent organisations in relation to the care and cure of RTT. There is no doubt that the level and type of services and support offered to individuals and families with RTT across Europe are disparate and inequitable at all stages of the healthcare pathway, (pre)diagnosis onwards. A few MS are well-served by knowledgeable and expert medical professionals, and/or multi-disciplinary expert centres but a far greater number are not. Several countries have invested in a registry for RTT and contribute to a wider European or international database, but this is by no means a universal given and, with a rare disease, maximum benefit from sharing of data must surely be gained by all individuals/countries contributing to a shared registry. Parent organisations provide crucial information, advice, support and training for fellow parents and for professionals where they can. In some cases, they are in a position to fund research or even to support expert centres with funding. In other cases, the parent associations are run on a voluntary basis without dedicated funding and are limited in what they are able to offer.

For those families where expertise in RTT is minimal in their own country, European policy in relation to rare diseases offers hope for the future, in particular through the Cross-Border Directive and EUCERD recommendations for RD ERNs and for CEs. The Rett Expertise Centres that already exist, together with other skilled and knowledgeable teams and practitioners, are well placed for inclusion within the broader RD ERNs, which could operate both within and across MS. From the proposed ERN groupings, it would seem most logical to include Rett Expertise Centres, whether they are stand-alone centres or organised under an umbrella such as ESRRRA, in group 5: 'Rare diseases of brain development and rare intellectual disabilities' [10] (table 1, p. 10). Co-ordinated RD ERNs, including RTT within their remit, would not only strengthen existing services for RTT but would also facilitate diagnosis, advice, support and treatments for individuals and families in countries that are currently under-resourced, as well as stimulating professional development and quality of care through the creation and sharing of clinical guidelines, models of best practice and training resources. Furthermore, referral of individuals for diagnosis and treatment between countries should be entirely possible.

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Chapter 3

Rett Syndrome and the Role of National Parent Associations within a European Context

Published as:

Townend, G.S., Smeets, E., van Waardenburg, D., van der Stel, R., van den Berg, M., van Kranen, H.J., & Curfs, L.M.G. (2015). Rett syndrome and the role of national parent associations within a European context. *Rare Diseases and Orphan Drugs*, 2(2), 17-26

Abstract

Rett syndrome (RTT) is a rare neurodevelopmental disorder arising from a genetic mutation on the X chromosome. In recent years there has been an increasing focus in Europe on developing links, both within and between countries, between researchers, clinicians, therapists, individuals with RTT and their families or caregivers in order to maximise approaches towards treatment and long-term-management of the disorder. This paper seeks to place RTT, especially the support of families living with RTT, in a European context. It explores the important role played by both the national Rett parent associations and the Rett expertise centres that exist in many of the Member States of the European Union and places the contribution of both within the context of European policy on rare diseases.

Keywords

Rett syndrome; Parent associations; Centres of expertise; European Union; European policy; Rare diseases; Rare disease registries.

Introduction

Rett syndrome (RTT) is a rare neurodevelopmental disorder thought to affect 1 in 9,000 – 15,000 live female births [1-4]. This is due to a genetic mutation on the X chromosome which is most commonly found in the *MECP2* gene [5-8] although other variants have been identified. The severity of the clinical presentation varies according to the specific mutation [9-14]. Typically, however, the syndrome is characterised by seemingly-normal development in the early months of life following which there is a noticeable regression of skills, beginning between 6 and 18 months of age [15]. A cascade of evolving clinical features has been delineated according to a series of stages [16, 17]. Individuals with RTT demonstrate a loss of motor and communication skills [18, 19], in large part due to the influence of dyspraxia which affects their ability to make purposeful movements; additional concomitant features generally include severe breathing abnormalities, epilepsy and scoliosis [20]. It is a severe, lifelong disorder which impacts greatly on quality of life and leads to a shortened life expectancy [21-24].

In 2007 Bird and colleagues first demonstrated that the symptoms of RTT could be reversed in mice [25]. Since then much research has been devoted to both the treatment and potential cure of RTT [26-29] as well as the development of more functional therapies which seek to enhance the participation and quality of life of individuals living with this rare disorder [30-37].

Both the literature and the number of clinicians worldwide with specialist knowledge and skills relating to this population are small but increasing, as is the number of multidisciplinary centres specialising in the care and management of individuals with RTT and their families. At the present time, however, there is huge variability in knowledge and expertise between countries and huge variability in clinical practices both between and within countries. There are few national and no internationally-agreed models for the delivery of clinical services to this population; neither are there international guidelines for the overall clinical management of the syndrome although these have been proposed for individual aspects, such as scoliosis [38] and growth and nutrition [39].

Within this global context, there is a growing recognition of the need to strengthen collaborations within and between professional and parent groups at both European and international levels, and it is clear that Rett parent associations can provide a valuable role in disseminating and sharing information and training, and in supporting both families and professionals. *Rett Syndrome Europe* (RSE)¹ has formed as an umbrella organisation for the European parent associations and, as a member of EURORDIS (the *European Rare Diseases Organisation*)² also makes a vital contribution to the debate on European policy in relation to rare diseases. Likewise, in recent years, professionals (researchers, clinicians and

¹ <http://www.rettsyndrome.eu/association-rse/europe/>

² <http://www.eurordis.org/>

therapists) from a number of expert centres across Europe have come together to form ESRRRA (the *European Scientific Rett Research Association*)³, a collaborative European platform for research focusing on RTT. Beyond Europe, international organisations such as *Rettsyndrome.org*⁴ similarly give invaluable impetus to harnessing and stimulating developments in knowledge and expertise and promoting a sense of community between families and professionals within this relatively small field.

This paper offers an overview of the situation relating to RTT in countries within the European Union (EU) and European Economic Area (EEA) as of 2015.

European Rett Syndrome Conferences

In 2009 the first European Rett Syndrome Congress was held in Milan, Italy. This was an important milestone in bringing together researchers, scientists, educators, therapists and families to explore aspects relating to then-current research and treatment of RTT. The value of such a pan-European format was recognised and a second European conference followed in Edinburgh in 2010. In 2013 this model was again repeated with the third European Rett Syndrome Conference (ERSCM2013). Entitled 'Research Update and Preventive Management', this three-day conference was held in Maastricht, The Netherlands, and attracted 340 participants from 31 countries, representing 19 Member States of the EU, two EEA states, and ten other countries. The wishes and needs of parents, as expressed by the Rett parent associations and Rett syndrome foundations, were central to the development of the programme. The conference proved to be an exciting and stimulating opportunity for the sharing and dissemination of information concerning the latest developments in scientific and medical research and therapies, with separate seminar streams offered for researchers and scientists and for therapists and families, in addition to shared sessions open to all.

During the 'parent track' there was a particular emphasis on fostering opportunities for networking and information exchange between the national Rett parent associations; sessions at both the beginning and end of the conference were devoted to the European parent associations sharing information on their countries whilst RSE also held its annual General Assembly during the conference. At the close of the conference the organising committee and RSE signed a joint statement declaring their support for the European Union policy on rare diseases and defining more precisely the wishes of the European parent organisations in relation to the care and cure of RTT.

Of the 21 EU and EEA Member States present at the conference, 18 parent associations offered a presentation during the conference. In addition, presentations were given by the Israeli and Russian Rett parent associations. Each country was asked to set the scene by

³ <http://www.europeanscientificrettresearchassociation.eu/>

⁴ <http://www.rettsyndrome.org/>

providing some basic national population statistics as well as statistics for RTT in that country, as far as available. Information on any Rett expertise centres or specialists in the field, together with an outline of the aims, activities and wishes of the parent association and/or foundation (if one existed) was also requested. The slides from these presentations can be accessed through the website of the Dutch Rett parent association (NRSV)⁵.

Key information relating to the Rett parent associations in the EU and EEA Member States is shown in Table 1, whilst Table 2 provides an overview of centres of expertise and/or main hospitals providing diagnosis and medical care/advice and/or conducting research into RTT. The information contained within the tables is as presented by the national parent associations during ERSCM2013, supplemented by information taken from the websites of the national parent associations and/or email contact with parent representatives/medical consultants from each of the countries (up to September 2015). Additional and/or updated information on the current situation in each country (including details of parent association activities) can be accessed via the website addresses listed in the tables.

The fourth European Congress on Rett Syndrome took place in Rome, Italy, during the last weekend of October 2015.

Comparisons Across Europe

As of 2015 between five and ten European countries have (to varying degrees) either a national Rett expertise centre or specialised multidisciplinary Rett clinics, some of which are embedded within centres for rare diseases. A number of experts and researchers from these centres collaborate through ESRR, as described above. Several countries have one or more hospitals providing a diagnostic service and/or one or more medical experts offering advice and clinical management of the syndrome, whilst other European countries have no experts in RTT and rely on services aimed at general disabilities (for further details see Table 2). In these cases, the role of the national parent association, where one exists, is especially crucial in supporting families and professionals alike.

All of the European parent associations listed in Table 1 exist to offer support and networking opportunities for families of individuals with RTT. They also see that they have an important role in disseminating information and raising awareness of RTT, both in keeping families up to date with new advances in research and in increasing the knowledge of professionals in their countries. The majority of associations are volunteer-led by parents and other family members; a few of the larger organisations are able to fund administrative and, occasionally, support staff, to bolster and extend the work of the parents. In some cases, they are also in position to fund research or even to support centres of expertise with funding. All but one of the existing parent associations host websites as a medium for sharing information and most use social media such as Facebook as a support mechanism.

⁵ <http://www.rett.nl/>

Table 1. EU & EEA Member States information: national population and Rett statistics (known and estimated), and parent association details.

Country ^a	Population ^b	Birth rate per 1,000 population ^b	Estimated number of girls born per year with RTT ^c	Number of families/ individuals known to have RTT (approximate in some cases) ^{d,e}	Parent association name & website
Austria	8.22 million	8.76	2.3 – 3.9	102 ^d	Österreichische Rett-Syndrom Gesellschaft (ÖRSG) Founded 1996 www.rett-syndrom.at Member of Pro-Rare Austria
Belgium	10.45 million	9.99	3.4 – 5.7	80 ^d	Belgische Rett Syndroom Vereniging (BRSV) Founded 1988 www.rettssyndrome.be
Bulgaria	6.92 million	8.92	2.0 – 3.3	No information available	No Rett Parent Association registered with RSE
Croatia	4.47 million	9.49	1.4 – 2.3	29 ^e	No Rett Parent Association registered with RSE
Cyprus	1.17 million (Republic & Northern Cyprus)	11.44	0.4 – 0.7	Several ^d (clinical rather than molecular diagnosis)	No Rett Parent Association registered with RSE <i>Pancyprian Association for Rare Genetic Disorders ('Unique Smiles')</i> offers support to families via Facebook
Czech Republic	10.63 million	9.79	3.4 - 5.6	50 ^d (unofficial)	<i>Rett Community Association</i> Founded 2004 www.rett-cz.com/cz Member of CAVO, Czech Association of Rare Diseases
Denmark	5.57 million	10.22	1.8 – 3.1	123 ^d	<i>Landsforeningen Rett Syndrom</i> Founded 1988 www.rett.dk Member of Rare Diseases Denmark
Estonia	1.26 million	10.29	0.4 – 0.7	No information available	No Rett Parent Association registered with RSE
Finland	5.27 million	10.35	1.8 – 3.0	60 ^d (unofficial)	<i>Rett ry – Rett Finland</i> (formerly <i>Autistien ja Rett-henkilöiden Tuki ry, AURE ry</i>) Founded 1989 www.aure.fi
France	66.26 million	12.49	26.9 – 44.9	523 ^d	<i>Association Française du Syndrome de Rett (AFSR)</i> Founded 1988 https://afsr.fr
Germany	82 million	8.42	22.1 – 36.8	623 ^d	<i>Elternhilfe für Kinder mit Rett-Syndrom in Deutschland e.V.</i> Founded 1987 www.rett.de

Country ^a	Population ^b	Birth rate per 1,000 population ^b	Estimated number of girls born per year with RTT ^c	Number of families/ individuals known to have RTT (approximate in some cases) ^{d,e}	Parent association name & website
Greece	11 million	8.8	3.1 – 5.1	No information available	Άγγελοι γης ('Angels on Earth') Founded 2011 www.rettgreece.gr Member of <i>Panhellenic Association of Rare Diseases</i>
Hungary	9.92 million	9.26	3.0 – 5.0	80 ^d	<i>Magyar Rett Szindróma Alapítvány</i> Founded 1995 www.rettszindroma.hu Member of <i>RIOSZ, National Association of Rare Diseases</i>
Iceland	317,350	13.09	0.14 – 0.23	2 ^d (verified through DNA analysis)	<i>Gudrun's Rett Syndrome Research Trust</i> Founded 2012 http://rettenglar.yolasite.com
Ireland	4.83 million	15.18	2.5 – 4.1	No information available	<i>The Rett Syndrome Association of Ireland</i> Founded 2003 http://rettsyndrome.ie/
Italy	61.68 million	8.84	17.7 – 29.4	660 ^e	<i>Associazione Italiana Rett (AIRETT)</i> Founded 1990 www.airett.it
Latvia	2.17 million	9.79	0.7 – 1.2	No information available	No Rett Parent Association registered with RSE
Lithuania	3.51 million	9.36	1.1 – 1.8	No information available	No Rett Parent Association registered with RSE <i>Lietuvos autizmo asociacija "Lietaus vaikai" (Lithuania Autism Association)</i> offers support to families Founded 2013 www.lietausvaikai.lt
Luxembourg	521,000	11.75	0.2 – 0.3	No information available	No Rett Parent Association registered with RSE <i>Autisme Luxembourg asbl</i> offers support to families Founded 1981 http://www.autisme.lu <i>ALAN – Rare Diseases Luxembourg</i> also supports families Founded 1998, rare disease included from 2005 http://www.alan.lu
Malta	412,655	10.24	0.1 – 0.2	4 ^d	No Rett Parent Association registered with RSE

Country ^a	Population ^b	Birth rate per 1,000 population ^b	Estimated number of girls born per year with RTT ^c	Number of families/ individuals known to have RTT (approximate in some cases) ^{d,e}	Parent association name & website
Netherlands	16.88 million	10.83	5.9 – 9.9	175 ^d	<i>Nederlands Rett Syndroom Vereniging (NRSV)</i> Founded 2008 www.rett.nl <i>Stichting Terre - Dutch Rett Syndrome Foundation</i> Founded 2008 www.stichtingterre.nl
Norway	5.15 million	12.09	2.01 – 3.36	130 ^d	<i>Norsk Forening for Rett Syndrom</i> Founded 1987 www.rettssyndrom.no
Poland	38.35 million	9.77	12.1 – 20.2	70 ^d	<i>Ogólnopolskie Stowarzyszenie Pomocy Osobom Z Zespołem Retta (OSPOZZR)</i> Founded 1997 http://rettssyndrom.pl
Portugal	10.81 million	9.42	3.3 – 5.5	No information available	<i>Associação Nacional de Pais e Amigos Rett (ANPAR)</i> Founded 2002 http://anpar.planetaclix.pt
Romania	21.73 million	9.27	6.5 – 10.9	16 ^e	<i>Asociația "Un inger pentru ingeri" ('An angel for the angels')</i> Founded 2013 www.asociațiaungerpentruingeri.ro
Slovakia	5.44 million	10.01	1.8 – 2.9	30 ^d	<i>Rett Slovakia (Nadacia pre pomoc ľuďom postihnutým Rettovým syndrómom-Slovensko)</i> Founded 2002 No website
Slovenia	1.99 million	8.54	0.6 – 0.9	No information available	<i>Tihi angeli ('Quiet angels')</i> - not currently active
Spain	47.74 million	9.88	15.2 – 25.3	426 ^e	<i>Asociación Española de Síndrome de Rett</i> Founded 1992 www.rett.es <i>Asociación Catalana del Síndrome de Rett</i> www.rettcatalana.es Members of the Spanish Federation of Rare Diseases
Sweden	9.72 million	11.92	3.8 – 6.3	250 ^d	<i>Rett syndrome i Sverige (RSIS)</i> Founded 1997 www.rsis.se

Country ^a	Population ^b	Birth rate per 1,000 population ^b	Estimated number of girls born per year with RTT ^c	Number of families/ individuals known to have RTT (approximate in some cases) ^{d,e}	Parent association name & website
UK	63.74 million	12.22	25.3 – 42.2	255 ^e	<p>Rett UK</p> <p>Founded 1985 http://www.rettuk.org</p> <p>Member of <i>Rett Disorders Alliance of the UK</i></p> <p>Founded 2015 Includes: <i>Rett UK, Reverse Rett, Cure Rett, Reverse MECP2, FOXG1 UK, CDKL5 UK, Rett Education UK</i></p>

Additional information on each country (including details of Parent Association activities) can be accessed via the Parent Association websites as listed in this table or via the website of Rett Syndrome Europe (<http://www.rett Syndrome Europe.eu/association-rse/europe/>). In addition, the slides which were presented by national Parent Associations during the 'Country Updates' sessions of ERSCM2013 can be accessed via: <http://www.rett.nl/>.

^a = Countries are arranged in alphabetical order. Liechtenstein is not included.

^b = Country population as of mid-2014, annual crude birth rate, and sex ratio at birth are all taken from: <http://www.indexmundi.com/europe.html>.

^c = Adjusted per country according to sex ratio at birth (varying between 1.04 – 1.07 male(s)/female) and calculated to show upper and lower potential limits taking into account an estimated incidence of Rett syndrome as 1 per 9,000 – 15,000 live female births.

^d = Numbers of 'known' individuals/families as reported by the national parent associations.

^e = Numbers of individuals registered on the Rett Database Network as of September 2015 (shown where numbers of 'known' individuals were not available through the Parent Association), see: <https://www.rett-databasenetwork.org/>.

Table 2. Overview of centres of expertise and hospitals providing diagnosis, medical care and advice for Rett syndrome in EU & EEA Member States.

Country	Overview of Experts and/or Expertise Centres
Austria	<p>Expertise Centre for RTT – under development</p> <p>Diagnosis and medical care/advice – Departments of Medical Genetics and Paediatric and Adolescent Neurology, Medical University of Vienna, in cooperation with other specialists/clinics</p> <p>Research – Medical University of Graz</p>
Belgium	<p>Diagnosis, medical care/advice – Centre for Developmental Disabilities, University Hospital, Leuven follows up all rare diseases and disorders with developmental delay, other University Hospitals across Belgium offer support for epilepsy, scoliosis, nutrition</p> <p>Second opinions/medical care/advice – Rett Expertise Centre Maastricht (Netherlands) may be consulted</p>
Bulgaria	<p>Diagnosis, medical care/advice – Paediatric Neurology Clinic of St Nahum Hospital in Sofia</p>

Country	Overview of Experts and/or Expertise Centres
Croatia	Diagnosis – Institute Rudjer Boskovic and the Children's Hospital Zagreb Medical care/advice – Centre of Expertise for Congenital Disorders at the Children's Hospital, Zagreb, and Neuropaediatric Departments of the Clinical Hospitals in Zagreb, Split, Osijek and Rijeka
Cyprus	Diagnosis, medical care/advice, research – Makarios Children's Hospital and Cyprus Institute of Neurology and Genetics
Czech Republic	Diagnosis, medical/paramedical care and advice – University Hospital of Motol, Prague A few schools/day care centres offer education and consultancy specific to RTT
Denmark	Expertise Centre for RTT – Danish Centre for Rett Syndrome (part of the Kennedy Centre at Glostrup) http://www.kennedy.dk Diagnosis, medical/paramedical care, advice, research – multidisciplinary team in Glostrup, in cooperation with local hospitals
Estonia	Diagnosis and medical care/advice – consultant at Tartu University Hospital, Children's Clinic
Finland	Diagnosis – Child Neurology Departments at University Hospitals across Finland (Rare Disease Expertise Centres will be established at all University Hospitals, currently available at Helsinki University Central Hospital and in Turku) Medical care/advice – child neurologist with a special interest in RTT at Children's Hospital of Helsinki, basic health care provided by hospitals across Finland, Government-funded therapy provided weekly according to each individual's personal rehabilitation plan
France	Expertise Centre for RTT – due to open at Necker Enfants Malades in Paris in 2015 Diagnosis, medical/paramedical care, advice, research – a range of experts/teams at various hospitals across France, e.g. hospitals in Paris, Marseille, Douai, Nancy, Tours, Barr, Bordeaux, Dijon
Germany	Diagnosis, medical care/advice – clinics in Kassel, Göttingen and Langen-Depstedt
Greece	Diagnosis, medical care/advice – several doctors across Greece have an interest in RTT
Hungary	Diagnosis and research – Rett Centre/Medical Genetics, University of Pécs <i>PART</i> and <i>DROP</i> programmes for families (therapy and education) and professionals (professional development/training) arranged by parent association
Iceland	Expertise Centre for RTT – State Diagnostic and Counselling Centre (SDCC) http://www.greining.is Diagnosis, medical care/advice – collaboration between SDCC, neurology department of the Children's Hospital, and Benefit Society for Children with Disabilities
Ireland	Diagnosis – National Centre for Medical Genetics, Dublin Medical care and advice – hospitals across Ireland offer general support, some families seek more specific assessment and advice from UK Rett Clinics

Country	Overview of Experts and/or Expertise Centres
Italy	Expertise centres for RTT – Genoa, Milan, Rome, Siena, Messina Diagnosis, medical care/advice, research – range of consultants and researchers at centres in Genoa, Milan, Rome, Siena, Messina Founding member of ESRRA
Latvia	Diagnosis, medical care/advice – Children’s Clinical University Hospital, Riga is the only hospital in Latvia that offers specialised multi-disciplinary treatment and care for rare diseases, the Medical Genetics Department provides genetic testing and counselling across all ages
Lithuania	Diagnosis – Coordinating Centre for Rare Paediatric Diseases, Children’s Hospital Vilnius Medical care and advice – Child Development Centre, Vilnius and hospitals across Lithuania offer general support
Luxembourg	Diagnosis, medical care and advice – neurologist at Centre Hospitalier de Luxembourg, supported by experts in neighbouring countries e.g. Rett Expertise Centre Maastricht (Netherlands), CHU de Liège (Belgium)
Malta	Diagnosis, medical care/advice – included within Malta’s National Care for Disabled Persons (KNPD) Education/therapy – <i>INSP/RE</i> Foundation offers holistic programmes and services to children and adults with various disabilities http://inspire.org.mt
Netherlands	Expertise Centre for RTT – Rett Expertise Centre Maastricht (national reference centre recognised by Dutch government) http://gkc.daily-cms.com/pages/Rett_syndrome Diagnosis, medical care/advice, research – multidisciplinary team in Maastricht in cooperation with other (University) Hospitals and local teams Founding member of ESRRA
Norway	Expertise Centre for RTT – Frambu Resource Centre for Rare Disorders (national resource centre for people with rare disorders and disabilities) http://www.frambu.no/retts-syndrom Diagnosis, medical care/advice and research – multidisciplinary team at Frambu
Poland	Diagnosis – Medical Universities in Bialystok, Warsaw, Krakow Medical care/advice – provided by centres for general disabilities (e.g. cerebral palsy, autism) with a (small) number of medical specialists who have an interest in RTT based in University Medical Centres across Poland
Portugal	Diagnosis, medical care/advice – Paediatric Neurology Departments of Hospital de Santo Antonio, Porto (also provides second opinions) and hospitals in Coimbra and Lisbon
Romania	Diagnosis – Carol Davila University of Medicine, Bucharest or hospitals in other countries e.g. Bulgaria, Hungary, Spain Medical care/advice – Paediatric Neurology Department of Carol Davila University manages seizures, hyperventilation problems, kinetic and psychotherapy programmes, other hospitals across Romania offer general support
Slovakia	Diagnosis – Comenius University Hospital in Bratislava or via University Hospital of Motol, Prague (Czech Republic) Medical care/advice – hospitals across Slovakia offer general support

Country	Overview of Experts and/or Expertise Centres
Slovenia	Diagnosis, medical care/advice – Department of Child, Adolescent and Developmental Neurology, University Children's Hospital, Ljubljana sees all cases of RTT and organises further therapies through local hospitals/teams
Spain	Expert Centre for RTT – Hospital Sant Joan de Deu in Barcelona Diagnosis, medical care/advice and research – child neurologists and local teams at hospitals across Spain, in cooperation with Sant Joan de Deu
Sweden	Expertise Centre for RTT – Swedish Rett Centre in Östersund www.rettcenter.se Diagnosis, medical care/advice and research – multidisciplinary team at Östersund, in cooperation with other hospitals/local teams Founding member of ESRRA See also – Ågrenska, National Competence Centre for Rare Diseases http://www.agrenska.se
UK	Diagnosis, medical care/advice and research – specialist multidisciplinary RTT clinics in London, Manchester, Nottingham and Cardiff, in cooperation with local hospitals/teams Founding member of ESRRA

The information presented in this table is as reported by the national parent associations during ERSCM2013, with additional information taken from the websites of the national parent associations and/or representatives from the countries (as of September 2015). Further updates on the current situation in each country can be accessed through the website of the relevant parent association (addresses shown in Table 1), any of the websites listed in the table below, or the website of Rett Syndrome Europe (<http://www.rettsyndrome.eu/association-rse/europe/>).

Countries are listed in alphabetical order. Liechtenstein is not included.

Furthermore, a number of countries benefit from Rett foundations or research trusts which may exist in place of or in addition to the national parent association. The focus of such organisations is to raise funds for and to promote basic and applied research in relation to the treatment and cure of RTT. For example: in the Netherlands, the Stichting Terre-Dutch Rett Syndrome Foundation and in Iceland, Gudrun's Rett Syndrome Research Trust, whilst in the UK, the Rett Disorders Alliance of the UK was formed in July 2015, a collaboration of organisations working with and for the benefit of RTT and RTT-like disorders. This alliance comprises: Rett UK, Reverse Rett, Cure Rett, Reverse MECP2, FOXP1 UK, CDKL5 UK, and Rett Education UK. International collaborations are also evident. For example, Reverse Rett (formerly Rett Syndrome Research Trust UK) works in partnership with the US-based Rett Syndrome Research Trust and Cure Rett is in partnership with Rettsyndrome.org in the US.

Databases and Registries

Several European countries have some form of national database or registry specifically for RTT, for example, France, Italy, Portugal, Spain, UK⁶. These and others also contribute to larger European or international RTT databases, for example, the Rett Database Network⁷ and/or InterRett⁸. As of September 2015, the Rett Database Network held information on just over 2,000 individuals from 14 countries across Europe and further afield.

In addition, a number of mutation databases exist, which, in the era of 'next generation sequencing' (NGS) [40] are invaluable in contributing to an understanding of the biology associated with rare diseases such as RTT [41]. One such database to which a number of European (and other) countries contribute is RettBase, a MECP2 variation database, initiated by John Christodoulou and colleagues⁹ [42]. Recently, information from this database has been incorporated into LOVD 3.0 (Leiden (open) Source Variation Database)¹⁰ [43], a locus-specific database which seeks to connect NGS-driven collections built upon whole exome- and whole genome sequencing, such as ClinVar¹¹ and EVS¹², and global initiatives such as the Global Alliance for Genomics and Health¹³.

⁶ Some of these registries are listed on Orphanet:

[http://www.orpha.net/consor/cgibin/ResearchTrials_RegistriesMaterials.php?Ing=EN&type_list=researchtrials_search_simple_shd&data_id=91&Disease\(s\)/group%20of%20diseases=Rettsyndrome&search=ResearchTrials_RegistriesMaterials_Simple&ChdId=91&Ing=EN&ResearchTrials_ResearchTrials_RegistriesMaterials_diseaseGroup=rettsyndrome&ResearchTrials_ResearchTrials_RegistriesMaterials_diseaseType=Pat&ResearchTrials_ResearchTrials_RegistriesMaterials_RegCategory=NN&ResearchTrials_ResearchTrials_RegistriesMaterials_country=NN&ResearchTrials_ResearchTrials_RegistriesMaterials_GeographicType=null&ResearchType=Reg](http://www.orpha.net/consor/cgibin/ResearchTrials_RegistriesMaterials.php?Ing=EN&type_list=researchtrials_search_simple_shd&data_id=91&Disease(s)/group%20of%20diseases=Rettsyndrome&search=ResearchTrials_RegistriesMaterials_Simple&ChdId=91&Ing=EN&ResearchTrials_ResearchTrials_RegistriesMaterials_diseaseGroup=rettsyndrome&ResearchTrials_ResearchTrials_RegistriesMaterials_diseaseType=Pat&ResearchTrials_ResearchTrials_RegistriesMaterials_RegCategory=NN&ResearchTrials_ResearchTrials_RegistriesMaterials_country=NN&ResearchTrials_ResearchTrials_RegistriesMaterials_GeographicType=null&ResearchType=Reg)

⁷ <https://www.rettbasenetwork.org/>

⁸ <http://www.aussierett.org.au/>

⁹ <http://mecp2.chw.edu.au/>

¹⁰ <http://www.lovd.nl/3.0/home>

¹¹ <http://www.ncbi.nlm.nih.gov/clinvar/>

¹² <http://evs.gs.washington.edu/EVS/>

¹³ <http://genomicsandhealth.org>

LOVD's capability to include phenotypic HPO-based information is also considered to be one of its strengths¹⁴.

Wishes and Future Aims of the European Parent Associations

In general terms, all parent associations express a wish for early diagnosis and better medical, therapeutic and care services, increased support for families and increased dissemination and application of evidence-based knowledge in order to improve quality of life for individuals with RTT and their families. All families ultimately hope for a 'cure' for RTT.

In more specific terms, they call for further research and funding for research into areas such as epilepsy, scoliosis, brainstem dysfunction, genetics and stem cell research. Several associations hope for increased recognition of the syndrome within the health insurance system and for increased funding to enable the buying or renting/loan of medical equipment and communication aids. There is also a desire expressed by all associations for collaboration with and between scientific researchers, increased contact and networking between national parent associations, collaboration between Rett expertise centres in different countries and the establishment of national centres of expertise in countries where they do not currently exist. Furthermore, they advocate for the building up of pan-European specialist networks, linking medical experts and therapists within and between countries and facilitating the training and recruiting of specialists in countries where they are currently lacking.

European Policy on Rare Diseases

Of particular relevance at the time of ERSCM2013 were the provisions for the creation of 'European reference networks' (ERNs) written into Articles 12 and 13 of the 2011 Cross-Border Healthcare Directive (Directive 2011/24/EU)¹⁵, which built on earlier recommendations made by the Council of the European Union for Member States to develop their own national plans for rare diseases¹⁶. Quality criteria for 'Centres of Expertise for Rare Diseases' were also provided by the European Union Committee of Experts on Rare Diseases (EUCERD) in 2011¹⁷, following which core indicators for the aforementioned national plans/strategies¹⁸ and further recommendations for RD patient

¹⁴ <http://www.human-phenotype-ontology.github.io/about.html>

¹⁵ See <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:en:PDF>

¹⁶ Council Recommendation of June 8, 2009, on an action in the field of rare diseases (2009/C 151/02).

¹⁷ See <http://www.EUCERD.eu/upload/file/EUCERDRecommendationCE.pdf>

¹⁸ See http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf

registration and data collection¹⁹ and for Rare Disease ERNs²⁰ were released by EUCERD in 2013. Included in these recommendations was recognition of the integral role of patient/parent organisations.

It was in support of these policy developments, as well as to convey the more specific wishes of the Rett parent associations as outlined above, that the joint statement aimed at the Directorate General for Health and Consumers Affairs of the European Commission was signed at the end of the third European Rett Syndrome Conference in October 2013.

Following publication of the European Commission's Delegated Decision (2014/287/EU)²¹ and Implementing Decision (2014/286/EU)²² in March 2014, further clarification on the structure of RD ERNs was provided through a EUCERD joint action workshop set up to review progress in Member States in October 2014²³. During this meeting, the suggested grouping of rare diseases within the new structure of ERNs was first promulgated and in June 2015 the final decision of the EC Expert Group on Rare Diseases²⁴ regarding "the grouping of RD into thematic networks and the necessity of a patient-centred approach to RD ERNs" (*Addendum*, p.2) was published as an Addendum²⁵ to the EUCERD Recommendations of January 2013. According to these groupings RTT would most naturally seem to sit within an ERN for 'Rare neurological diseases' (*Addendum*, p.8). A further account of recent developments in European policy and their implications for RTT can be found in Townend et al, 2015 [40] whilst a commentary on the challenges and opportunities to be offered by the development of ERNs can be found in Marciano et al, 2015 [44].

Discussion

The European Commission's policy on rare diseases provides significant political leverage within the Member States of the EU in the quest to raise awareness, to promote research and develop a stronger knowledge base, and to provide more equitable, higher quality services and support for individuals and families affected by rare disorders like RTT. On its own it is unlikely that any rare disorder would be high on the agenda of a national government. The European Commission's inclusion of rare diseases within Articles 12 and 13 of the Cross-Border Directive and the subsequent recommendations of EUCERD are, however, clear signals that minority health groups cannot and should not be ignored.

¹⁹ See http://www.eucerd.eu/wpcontent/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

²⁰ See http://www.eucerd.eu/?post_type=document&p=2207

²¹ See http://ec.europa.eu/health/ern/docs/ern_delegateddecision_20140310_en.pdf

²² See http://ec.europa.eu/health/ern/docs/ern_implementingdecision_20140310_en.pdf

²³ See http://www.eucerd.eu/wp-content/uploads/2015/02/WP8Workshop_ERN_2014.pdf

²⁴ EUCERD's mandate ended in July 2013 and was replaced from 2014 by the EC Expert Group on Rare Diseases. The final meeting of the EUCERD Joint Action was on 15th September 2015

²⁵ See http://ec.europa.eu/health/rare_diseases/docs/20150610_erns_eucerdaddendum_en.pdf

Furthermore, pan-European collaboration between stakeholders – parents, professionals (clinicians, therapists, educators), researchers – is recognised as an integral and fundamental requirement. Within this context, umbrella organisations such as ESRRA, as a collaboration of professionals and researchers, and RSE, as a collaboration of parent associations, have important roles to play whilst European (as well as international) conferences offer valuable opportunities for these groups to come together to engage in discussion and dissemination of latest research, treatment and management techniques. A commitment by all EU countries to the sharing of clinical data through pan-European (and/or international) registries/databases for rare diseases such as RTT is also a vital step in the collaborative endeavour.

There have been a number of attempts to construct (genetic) databases in relation to RTT, at country-based, European and international levels [42-43, 45-47]. Where these do exist they prove valuable sources of data for research purposes [21, 23, 24, 48-50]. At present, however, most countries are unable to report definitive figures for numbers of individuals diagnosed with RTT in their country. In part this is due to the fact that some individuals are diagnosed on the basis of clinical symptoms alone and some are diagnosed following genetic analysis. Even in the case of genetic analysis there are a number of possible mutations and the accuracy of diagnosis may depend upon the test(s) that are performed. In any case, it is clear from studies which suggest the likely incidence and prevalence rates of RTT that there are large numbers of undiagnosed individuals in every country, even when services are relatively well-coordinated and the syndrome is well-known amongst the professional community. In the near future, however, the application of new molecular techniques such as whole exome- and whole genome sequencing, especially if applied to new-born bloodspot screening, may lead to the detection of *MECP2* mutations even before the characteristic clinical features of Rett syndrome appear²⁶. Of course, the blanket application of such screening should only be considered if the early findings of the pilots are clinically actionable.

The reversal of the symptoms of RTT in mice has excited interest amongst families such that the ultimate goal in the minds of most families, and hence, most associations, is to find the ‘cure’. Some of the larger parent associations are in a position to contribute funding towards basic research in this area as well as being in a stronger position to lobby politically within their own countries for recognition of the syndrome. Families and associations are realistic, however, and recognise that a cure will not be forthcoming immediately. Thus they aim for a better quality of life for their children (of whatever age) in the here and now. This translates into parent associations acting as support networks for families, sharing knowledge and information, offering training where they are in a position to do so and pushing for the creation of centres of expertise and networks of knowledgeable and specialised professionals wherever possible. Few of the parent associations receive state

²⁶ <http://www.genomes2people.org/babyseqproject/>

funding and rely on fund-raising, donations and grants. The level to which this can be achieved naturally varies between countries, leading to disparities in services and support between countries. National parent associations gain strength in banding together to form a strong European network (as seen, for example, in RSE), both for lobbying purposes at a European level and as a practical way for countries to offer support to each other. The declaration signed by RSE and the conference organising committee on the final day of ERSCM2013 gave a clear signal that parents across Europe are united in their determination to see the ambitions of the European Commission policy on rare diseases, as well as their own specific wishes in relation to the treatment and cure of RTT, realised.

A co-ordinated European Reference Network for 'Rare neurological diseases', which includes RTT within its remit, will strengthen existing services for RTT, facilitate diagnosis, advice and support for individuals and families in countries which are currently under-resourced, and will allow for the referral of individuals between countries in order to seek diagnosis and treatment. In addition, the model established by the first four European Rett Syndrome Conferences, bringing together professionals and families to share updates on the most recent developments in research, treatment and management of RTT, has set an invaluable precedent which should be continued. Such pan-European collaborations can only be to the benefit of individuals with RTT and their families.

Competing Interest

None declared.

Acknowledgements

The authors wish to thank the members of the national Rett parent associations across Europe, Rett Syndrome Europe (RSE) and the European Scientific Rett Research Association (ESRRA). Also Jeremy Dawson (Professor in Health Management, School of Health and Related Research, University of Sheffield, UK).

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Chapter 4

MECP2 Variation in Rett Syndrome – an Overview of Current Coverage of Genetic and Phenotype Data within Existing Databases

Published as:

Townend, G.S.[#], Ehrhart, F.[#], van Kranen, H.J., Wilkinson, M., Jacobsen, A., Roos, M., Willighagen, E.L., van Enckevort, D., Evelo, C.T., & Curfs, L.M.G. (2018). *MECP2* variation in Rett syndrome - An overview of current coverage of genetic and phenotype data within existing databases. *Human Mutation*, 39(7), 914-924. doi:10.1002/humu.23542
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Abstract

Rett syndrome (RTT) is a monogenic rare disorder that causes severe neurological problems. In most cases it results from a loss of function mutation in the gene encoding methyl-CPG-binding protein 2 (*MECP2*). Currently, about 900 unique *MECP2* variations (benign and pathogenic) have been identified and it is suspected that the different mutations contribute to different levels of disease severity. For researchers and clinicians, it is important that genotype-phenotype information is available to identify disease-causing mutations for diagnosis, to aid in clinical management of the disorder, and to provide counselling for parents. In this study, 13 genotype-phenotype databases were surveyed for their general functionality and availability of RTT-specific *MECP2* variation data. For each database we investigated findability and interoperability alongside practical user functionality, and type and amount of genetic and phenotype data. The main conclusions are that, as well as being challenging to find these databases and specific *MECP2* variants held within, interoperability is as yet poorly developed and requires effort to search across databases. Nevertheless, we found several thousand online database entries for *MECP2* variations and their associated phenotypes, diagnosis or predicted variant effects, which is a good starting point for researchers and clinicians who want to provide, annotate, and use the data.

Keywords

Databases; FAIR data; Genetic variation; *MECP2*; Phenotype; Rett syndrome.

Introduction

Rett syndrome (RTT, MIM# 312750) is one of 5,000 to 8,000 known rare diseases that together have been identified as affecting 6-8% of the world's population. Approximately 80% of these diseases have a genetic origin (Council Recommendation on an action in the field of rare diseases (2009/C 151/02, Recital 5). Most of these diseases are caused by pathological variants in one single, disease-specific gene. In the case of RTT this is in *MECP2*, an important regulator of neuronal development and function [1, 2]. At the present time, around 900 unique variations in *MECP2* have been identified [3]. To help distinguish between pathological and neutral genetic variants [4], scientists and clinicians collect genetic data and corresponding phenotypic information and make this information available in databases, which can be used for research and prognostic purposes. In this respect, RTT serves as example for any monogenic rare disease where, due to the limited number of individuals, a better understanding of the disease can be reached through combining data from different databases that may be housed at different institutions and in different countries. In recent years, the European Union's policy on rare diseases (e.g. Directive 2011/24/EU) has recognized the value of sharing information, knowledge and expertise and has generated a number of initiatives to encourage pan-European collaboration, for example, through the creation of European Reference Networks (ERNs) such as Intellectual disability TeleHealth And Congenital Anomalies (ITHACA), the ERN focused on rare congenital malformations and rare intellectual disability in which RTT is placed¹.

Generally, there are different types of databases for rare diseases: 1) Patient registries, containing i.a. patient data, genetic data, phenotype descriptions and information on medication. These are not normally open to the public. There are several data platforms, for example, RD-connect, which host patient registries with controlled access. 2) Genetic data repositories, for example, EGA (European Genome-Phenome Archive). These have been increasing in number since next-generation sequencing (NGS), and especially whole exome sequencing (WES), has been used as a clinical standard for the diagnosis of rare disorders and other suspected genetic disorders. 3) Genotype-phenotype databases that combine genetic data (e.g. DNA sequences, variants, genotypes) with phenotypic data. 4) Databases that store general information about genes, proteins, metabolites, their interactions and their mutation specific aberrations.

It is within this context that rare disease registries and databases have also been recognized by the European Union as “key instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning”².

¹ http://ec.europa.eu/health/sites/health/files/ern/docs/ernithaca_factsheet_en.pdf

² https://ec.europa.eu/health/rare_diseases/policy/registries_en

This study focusses on the genotype-phenotype databases. Several such databases have been developed and will be discussed here. The fundamental goal of these databases is to collect and provide access to data and knowledge to promote research into the functional and pathogenic significance of genetic variants [5, 6]. Critical for accurate analysis is the ability to distinguish between the disease-causing alleles and the abundance of benign variants or less important functional variants that co-occur in both normal and disease-affected individuals. One consequence of the increased power of NGS – often used for gene panels, WES and whole genome sequencing (WGS) – is the increased danger of incorrect assignment of pathogenicity, when compared with single gene analysis. For instance, a typical WES (e.g. in the context of suspected diagnosis of a rare monogenic disorder) may uncover up to 25,000 variants [7]. Elucidation of just a handful of pathogenic variants from the resulting thousands continues to be a major challenge in spite of the availability of standardized software solutions. The most effective way to start distinguishing benign from pathogenic variants is based on population frequencies of variants. In this approach, all variants occurring in the population at higher frequencies than the disease prevalence are considered benign. From the many recent initiatives to collect exome variants of individuals without clear disease phenotypes, the Exome Aggregation Consortium (ExAC) is the largest, containing more than 60,000 exomes [8]. In general, the population frequency information will reduce the number of candidate (pathogenic) mutations to a couple of hundred [7]. Further prioritization can then take place by employing tools such as PolyPhen and SIFT (Sorting Intolerant From Tolerant). Ensembl's Variant Effect Predictor tool [9] makes these aforementioned classic approaches available; it also includes a number of newer methods to distinguish between pathogenic, implicated, associated, damaging, and deleterious variants and/or those of unknown significance among the remaining variants. These next steps in the prioritization process are summarized by Lelieveld et al. [9]. The challenge of distinguishing disease-causing sequence variants from the many potentially functional variants in any human genome recently prompted MacArthur et al. [10] to propose guidelines for investigating causality of sequence variants in human disease. The proper setup and use of databases is one of the key issues they identified in order to be able to upload, store and find pathogenic and benign variants.

The results of the analysis of disease-causing variants also provides vital information, not just for scientists and researchers who are seeking to further knowledge and understanding of certain diseases, but for clinicians to make the correct diagnosis and provide genetic counselling and patient care. State of the art genotype-phenotype databases are of particular value and, among these, the so-called locus-specific mutation databases (LSDBs) (e.g. LOVD [11]) have served diagnosticians for many years by facilitating the interpretations of genetic variants [5, 6]. In addition to the LSDBs, a variety of other (clinically relevant) databases with a focus on genotype-phenotype relationships has emerged in recent years [9] and the need to integrate information from these databases has also generated many initiatives. The RD-Connect project provides a platform for the

rare disease community to find and share data and tools [12]. It includes a pipeline to harmonize variant annotation of rare disease genomes [13], registries of rare disease registries and biobanks (Gainotti et al., submitted), and bioinformatics tools. It is developed in collaboration with infrastructures such as ELIXIR³, BBMRI-ERIC (the infrastructure consortium for biobanks)⁴ [14], and the Global Alliance for Genomics and Health (GA4GH)⁵. The creation of GA4GH in 2013 represents one of the most prominent large-scale initiatives in this area. The goals and progress of this group were published recently (GA4GH, 2016).

To support both clinicians and researchers, we present in this paper an overview of a number of current genotype-phenotype databases. We evaluate their general structure and function for use in biomedical research, especially for researchers/clinicians who want to find ‘their’ mutation or intend to find a database in which to store their genotype-phenotype data. We give an indication of the findability and interoperability, the practical user functionality (up and download functions), the type and quantity of genotype and phenotype data available, and provide suggestions for future improvement.

Materials and Methods

Selection of Databases

The databases and meta/integrated databases in this survey were selected according to the following criteria:

1. The database contains genetic variation and associated phenotypic information (genotype-phenotype databases);
2. The genetic data are available in a processed form to enable a direct search for variations in a specific gene, region or disease (e.g. in the HGVS or reference SNP (rs) format, an identifier given by the database dbSNP);
3. The database is available online (with or without prior registration);
4. The database is available in English.

We do not claim complete coverage of all available databases; we focus on those which were findable online using search engines (e.g. Google) or listed in FairSharing.org (formerly known as BioSharing.org) or other meta-databases (RD-connect, bioCADDIE). We evaluated as a separate category certain meta or integrated databases, which in themselves contain no new or unique information, but instead try to integrate information from others. However, a number of RTT-specific databases, akin to patient registries, were not included in our evaluation as they require membership of the consortium and an agreement to input data to the database, or they grant permission on a case-by-case basis when the request to access data is part of a specific research project with prior approval

³ <https://www.elixir-europe.org/>

⁴ <http://www.bbmri-eric.eu/>

⁵ <http://genomicsandhealth.org>

from a medical ethical board. In some instances, a minimal level of data is accessible to qualified researchers through already existing data-sharing rules. These include the database associated with the longitudinal, population-based Australian Rett Syndrome Study (AussieRett)⁶ [15], the International Rett Syndrome Database (InterRett)⁷ [16], the Rett Database Network⁸ [17] and the database generated by the US Rett Syndrome Natural History Study (NHS)⁹ [18]. These databases generally contain cross-sectional and longitudinal natural history data that has been directly acquired from or input by individuals and their families, either by families completing a questionnaire or through direct examination of the individual by a clinician experienced in RTT. Such methods of data collection differ from the genotype-phenotype databases of interest in this paper.

Assessment of Database Properties and Function

Aspects of FAIR

The FAIR metrics are not yet fully developed (Schultes et al. in preparation) but as several of these aspects are interesting for the purposes of our evaluation we checked whether each database meets the basic FAIR principles described by Wilkinson et al. [19]. These principles define that data is: (i) *findable* if data or meta data are assigned unique identifiers, described with rich metadata, and registered or indexed in a searchable resource; (ii) *accessible* if the data are retrievable by their identifiers via a standardized communication protocol, the protocol itself is open, free, universally implementable and allows authentication and authorization, whilst, to prevent data being lost, metadata continues to be accessible even when the data is no longer available; (iii) *interoperable* if a suitable language for knowledge presentation and an established vocabulary (e.g. ontologies) are used, and, ideally, the (meta) data includes references to other data; and (iv) *reusable* if a clear and accessible data usage license is available, the data is correctly and sufficiently described using domain-relevant community standards, and data origin and history are included.

Up- and Download Functions

To investigate user functionality, we looked especially at the upload and download functions of each database. The upload functions were typically found in separate ‘submit’ pages or information was given on how or to whom the data should be sent. For download functionality we checked whether we could manually download search results, for example, a list of *MECP2* variants and which formats were possible for this. Additionally, we looked for the API description (if available).

⁶ <https://rett.telethonkids.org.au/about/aussierett/>

⁷ <https://rett.telethonkids.org.au/about/interrett/>; <https://interrett.ichr.uwa.edu.au/output/index.php>

⁸ <https://www.rettbasenetwork.org>

⁹ <https://www.rettssyndrome.org/research/clinical-trials/natural-history-study>

Form of Genetic and Phenotypic Data

Each database was investigated for the form in which genetic variation (e.g. HGVS or rs) and phenotype information (e.g. diagnosis, predicted pathogenicity scores, HPO terms etc.) is stored.

Assessment of RTT/*MECP2*-Specific Content

Total Numbers of *MECP2* Variants in the Database

The total number of entries for (unique) *MECP2* variants, or variants which are associated with RTT, was assessed in each database (status March 2018).

Availability of Five Selected Test Variants

To examine the coverage of *MECP2* variants in more detail, five *MECP2* mutations were selected and used to perform test searches within each database (Table 1).

Table 1. *MECP2* mutations selected for test database searches.

	Variant 1	Variant 2	Variant 3	Variant 4	Variant 5
Source	MBD hotspot mutation from [20]	Frequently reported nonsense mutation	Frequently reported missense mutation	WES variant from [21]	WGS variant from [22]
Genomic level (GRCh37)^a	g.153296882G>A	g.153296777G>A	g.153296363G>A	g.153296093_153296115del	g.153295929_153296514del
RNA level (NM_004992.3)	c.397C>T	c.502C>T	c.916C>T	c.1200_1222del	c.765_1350del
Protein level	p.(Arg133Cys)	p.(Arg168*)	p.(Arg306Cys)	p.(Pro401Argfs*8)	p.(Lys256Asnfs*31)

^aThe current genome build at the time of writing this article is GRCh38, but most databases were using GRCh37. For *MECP2*, there is a difference ranging from 735 to 659 kbp.

We decided upon three ‘classical’ variants: first, a well-known and well-described mutation – an MBD hotspot mutation – published by Zappella, et al. (2001) [20] and reviewed by Lyst & Bird (2015) [1]; and, second and third respectively, two of the most frequently reported nonsense and missense mutations. Finally, two mutations that were discovered more recently by WES and WGS: a 23 bp deletion in the C-terminus of *MECP2*, reported by Rauch et al. (2012) [21] after performing WES in a girl displaying a RTT-phenotype; and, an intra-exonic deletion, taken from Gilissen et al. (2014) [22], after WGS in a person described as having severe intellectual disability (IQ < 50), a commonly reported clinical phenotype of RTT [23]. The appearance of each of these five mutations in the selected databases was investigated.

Results

We identified nine standalone databases and four meta/integrated databases for evaluation (Table 2) and collected information by exploring their content. We checked for general database features and RTT-specific entries. In detail, we analyzed (a) the FAIR status, (b) the upload and download possibilities, (c) form of phenotype and genotype information, (d) the total number of entries relating to the *MECP2* gene or RTT, and (e) the coverage for the chosen *MECP2* mutations.

Database Properties

Aspects of FAIR

In general, the genetic variation or location databases were easier to find than the RTT-specific ones. Using Google as the search engine for “Rett syndrome database”, only RettBase [24, 25] or excluded databases such as InterRett and the Rett Syndrome Database Network (both of which do not allow direct online access to genotype-phenotype information) were immediately findable – and several publications about RTT databases (e.g. about the Italian Rett database and biobank [26]). Using more generic terms like “genotype phenotype database”, dbGAP (which is an archive for genotype-phenotype studies), DECIPHER and DisGeNET were found. A more specific search result was yielded using meta-databases for biomedical databases. Seven of the databases were findable on FairSharing.org using the tags “rare disease”, “genetic variation”, or “phenotype”. Others were mentioned in previous publications [9] or found through personal recommendation within the scientific community. Considering findability of variants within the database, most offered the possibility to search for variants using at least one of the nomenclatures recommended by the guidelines of the HGVS for genome, RNA or protein changes, or by rs identifiers. The Korean Mutation Database provided no option to search for specific variants, only searches by disease (or disease identifier) were possible. In most cases the databases investigated were publicly accessible; several, however, restricted access to members only (e.g. parts of Café Variome) or were commercial databases with pay to view content (HGMD) (Table 3).

FAIRness, for human users, was hindered by a variety of factors. For example, while many databases provided a search function, one of the core aspects of ‘F’ – that data records are uniquely identified – was frequently overlooked by providers. Often, there was found to be a preference for embedded javascript/AJAX ‘reveals’ of otherwise unidentified data, and/or incremental drill-down searches until only one result remained. Furthermore, impediments to the ‘I’ and ‘R’ elements of FAIRness – Interoperability and Reusability – were evident in the sparse use of ontological terms, use of ontological terms without indicating their source ontology, and lack of easy-to-find citation information for individual data points within aggregate data.

Table 2. Overview of databases included in the review.

Database and link	Contact	How to cite ^a	Short description
RTT-specific database			
RettBase	Prof. John Christodoulou and Rahul Krishnaraj	[24]	Specific focus on RTT. Database of genetic information about RTT patients. Contains mutation information about MECP2 as well as CDKL5 and FOXP1 which cause different syndromes (formerly named Rett-like syndromes).
Databases for genetic variations and phenotype information for diseases in general			
KMD KMD Rett Syndrome (Korean Mutation Database)	Contact via KCDC (Korea Centre for Disease Control and Prevention)	-	Genotype-disease database. Collection of disease-causing variants in genes.
ClinVar ClinVar (MECP2)	Mail	[29]	Genotype-phenotype database. Focus on disease-causing variants in genes.
HGMD “professional”	Contact (via public website)	[30]	Commercial genotype-phenotype database
Databases for all kinds of genetic variations and phenotype information			
LOVD LOVD3.0 MECP2 (Leiden Open Variation Database)	MECP2 curator: Henk van Kranen	[11]	Genetic variants database. Locus/gene specific, all genes.
DECIPHER (Database of genomic variation and Phenotype in Humans using Ensembl Resources)	Mail	[31]	Genotype – phenotype database. All genes.
EVS EVS (MECP2)	Mail	-	Genetic variants database. Originally those which contribute to heart, lung and blood disorders. Now open to all

(Exome Variant Server)				genes, linked to dbSNP and dbGAP.
ExAC Browser (Exome Aggregation Consortium)	Github Mail		[32]	Database/project to collect and harmonize whole exome sequencing data. Allows search for variants at certain locations or single genes, and direct search for variants.
dbSNP (NCBI Short Genetic Variations database) dbSNP (MECP2)	Mail		[33]	Genetic variation database. Collection of single nucleotide polymorphism (SNP) and an effect predictor score.
Integrated/meta-databases and genome browsers				
dbVAR dbVAR (MECP2)	Mail		[34, 35]	Database for genomic structural variations, including indels, mobile element insertions, duplications, inversions, translocations, and complex chromosomal arrangements.
EVA (European Variation Archive)	Mail		-	Variant browser. Allows search for variants of specific locations or genes.
Cafe Variome	Mail		[36]	Meta-database for genetic variants, genotype-phenotype databases. Links to 1000 Genomes Project, dbSNP, Diagnostic Variants, Diagnostic Mutation Database, The Frequency of Inherited Disorders Database, Finnish Disease, FORGE Canada Consortium, PhenCode, UniProt, Human Gene Mutation Database, Locus-specific Databases. Freely available, but some of the linked databases content is only available after registration.
DisGeNET	Mail		[37, 38]	Database for gene-disease and variant-disease associations. Imports data from curated databases like UniProt, ClinVar, GWAS Catalog etc.

^a Literature reference for database

Table 3. Description of database structure and information types.

Database	↑ Up- and ↓ Download of data API (if available)	Phenotype information available	Genotype information available
RettBase	↑ Submission of data by mail possible ↓ No download function, Web interface No API or similar	Information on whether RTT or not, distinguishes between classical, atypical, preserved speech, and forme fruste RTT, mental retardation (not Rett), Autism	According to HGVS change on the mRNA/cDNA level, RefSeq NM_004992 unless stated otherwise
KMD	↑ Submission of data by registered users ↓ No download function, Web interface No API or similar	Diagnosed with RTT using the OMIM identifier (= RTT/RTT preserved speech variant)	According to HGVS change on the mRNA/cDNA level and RefSeq
ClinVar ^a	↑ Possible, detailed submission templates and instructions available ↓ Download/export of search results in form of text files or UI lists possible API available here	Information on whether Pathogenic or not, Diagnosis, for example, RTT, Autism, X-linked mental retardation	According to HGVS change on the mRNA/cDNA level (mostly) and RefSeq
HGMD "professional"	↑ Not possible, HGMD has its own data acquisition resources ↓ Download and export possible (for registered paying users)	UMLS (ontology) HPO (ontology) OMIM SNOMED CT MeSH	Descriptive: e.g. 11kb deletion in exon 1-2, HGVS format in the detailed description
LOVD ^a	↑ Upload possible after registration with Submitter clearance ↓ Download of complete database possible, not for specific genes/search results, API available for LOVD 2.0, for LOVD 3.0 under construction	Variant effect predictor: '+' indicating the variant affects function, '+?' probably affects function, '-' does not affect function, '-?' probably does not affect function, '?' effect unknown, '.' effect not classified."	According to HGVS change on the mRNA/cDNA, DNA and protein level and RefSeq
DECIPHER	↑ Open upload, bulk upload templates ↓ Web interface, and "Anonymised consented DECIPHER data can be made available in the form of	Detailed phenotype description, using HPO annotations	According to HGVS change on the mRNA/cDNA level and Ensemble ID of transcript used (includes RefSeq)

	a downloadable encrypted file from a secure server under a data access agreement. Please see the section on data access agreement on the Data Sharing page.” API available here			
EVS	<ul style="list-style-type: none"> ↑ Data is exclusively from NHLBI GO Exome Sequencing Project (ESP) ↓ Bulk download files, download of specific gene variant information search results as text or VCF No API or similar 	Variant effect prediction by PolyPhen2	According to HGVS on the mRNA/cDNA and protein level, rs IDs	
ExAC Browser	<ul style="list-style-type: none"> ↑ No upload possible, ExAC includes data from a list of projects ↓ Export of variation table as CSV possible API available here 	Variant effect prediction: Consequence of variation, for example, intronic variation, and consequence of protein aa change	rs IDs, genomic position, RefSeq and allele	
dbSNP ^a	<ul style="list-style-type: none"> ↑ Submission possible either directly or via EVA, dbGAP or ClinVar ↓ Possible, “Send to file” function for search results, batch query function for machine readability API at NCBI variant reporter 	Variant effect prediction, consequences like, for example, intronic variation, and consequence of phenotype, for example, increased susceptibility to diseases, is given. No RTT mutations are yet available.	rs IDs, HGVS (mRNA/cDNA)	
dbVAR ^a	<ul style="list-style-type: none"> ↑ Possible, no clinical data (ClinVar), no sensitive data (dbGAP) ↓ “Send-to-file” function API at NCBI variant reporter 	Clinical Assertion: pathogenic/uncertain significance	rs ID and allele	
EVA ^a	<ul style="list-style-type: none"> ↑ Open to everyone, submission guidelines ↓ Free – Export function (CSV), API available here 	Variant effect prediction by PolyPhen2/SIFT	rs IDs and allele	
Cafe Variome	<ul style="list-style-type: none"> ↑ Upload direct to Café Variome “hosted” or “in-a-box” ↓ Export of search results in different formats (CSV, html, LOVD...) 	dbSNP: “phenotype” column, no entries HGMD: no phenotype data Locus specific: no phenotype data	dbSNP: HGVS (mRNA/cDNA) allele and RefSeq HGMD: no variant data visible Locus specific: HGVS (mRNA/cDNA) allele and RefSeq	

	API available here	PhenCode: phenotype entry for 1/5 of entries: Diagnosis (RTT, X-linked mental retardation) Uniprot: same as PhenCode	PhenCode: HGVS (mRNA/cDNA), Reference links to original data source Uniprot: HGVS (mRNA/cDNA), reference links to UniProt ID
DisGeNET #	↑ No submission, adding of data by text mining and other databases ↓ Download of search results possible in different formats (download page here), provides a SPARQL endpoint	Diagnosis	rs IDs

^aFindable at *FairSharing.org*

On the positive side of FAIRness for humans, however, the terms of data access and re-use, for example, licensing and use for further studies, were reasonably well implemented in most databases. Not all data could be accessed and reused but the terms and conditions of use were clearly presented and a contact person or consortium was given.

FAIRness for machines was not evaluated, as, in most cases, the data providers made little or no effort to support automated accessibility or interoperability. The notable exception was DisGeNET, with its adoption of nanopublications (data structures that link data, data-provenance and citation-related information in a manner that can easily be interpreted by machines [27]), and provision of a SPARQL (SPARQL Protocol and RDF Query Language) query interface for these nanopublications [28]. Where available, a link to each database's API is given in Table 3.

Up and Download Functionality

It was possible to download or export search results as txt, CSV, RDF, XML, or other formats in ClinVar, EVS, EVA, ExAC, Café Variome, dbSNP, dbVAR, and DisGeNET (Table 3). For DECIPHER, the exporting of data to a file was possible upon request, and in HGMD for paying users. Several databases were found to encourage and accept data submission and provide upload functions or submission contacts. However, others were more restricted in this. For example, DisGeNET retrieves data from other (curated) databases and does not allow direct upload, EVS and ExAC have a defined list of sources (e.g. projects) from which the data is provided, and HGMD has its own data retrieval pipeline.

Genotype and Phenotype Information Format

Currently, there are two major forms in which genetic variants are given in databases: HGVS nomenclature and rs identifier. Four databases give only the rs ID (three of them include the respective allele), seven (including all Café Variome entries) only HGVS, and two both (Table 3).

The extent to which phenotype information is given was found to vary between the different databases (Table 3). Generally, there is a distinction between diagnosis-based information (six databases out of 13), phenotype (two, including HPO annotation) and predicted pathogenicity scores (PolyPhen/SIFT) (six). For example, ClinVar and PhenCode (PhenCode available via Café Variome) give the clinical diagnosis (e.g. RTT) including variants (e.g. RTT, preserved speech variant) while genetic variant databases provide other information. For example, LOVD, shows whether a variant is pathogenic (severe (+/+) or minor (-/+)) or not (-/-) based on the PolyPhen score; this is also the case in EVS. DECIPHER and HGMD provide detailed phenotypic information which is properly annotated using an ontology (HPO). HGMD in fact provides several options (diagnosis and phenotype). With regard to the RTT-specific databases, a search of RettBase yielded only information on the diagnosis (with variants), but no details about the associated phenotype (e.g. epilepsy, scoliosis, medication).

RTT-Specific Information

Total Number of MECP2 Entries

The greatest number of *MECP2* entries were found in RettBase (4738) (Table 4). dbSNP and LOVD both offer around 4500 entries (4229 and 4588), ClinVar 1145. Most other databases offer a few hundred *MECP2* entries. EVS, EVA, dbSNP, dbVAR, ClinVar and the ExAC Browser exchange information. DisGeNET imports information from ClinVar, so provides nothing new (Table 2).

Availability of the Five Test Variants

We used the mutations listed in Table 1 to perform a test search in the selected databases. The first three mutations, which are well-known, and in literature well-described mutations (c.397C>T, c.502C>T, and c.916C>T) were found most abundantly, with over 400 entries in almost all databases. The fourth (c.1200_1222del) was not found at all, and the fifth (c.765_1350del) was found only twice, in LOVD (*MECP2* gene homepage) and HGMD. These last two are derived from NGS studies indicating that the data submission pipelines of this data to genotype-phenotype databases are not yet that well established.

Discussion

In this study, we surveyed currently available genotype-phenotype databases using *MECP2* variants in RTT as a test case. We assessed the database structures and functionality and gave an overview of the available data on RTT, *MECP2* variants and their associated phenotypic data, with the aim of enabling data producers and data users to select a database which fits best with their needs to store, look up, and re-use available data.

Limited Availability of *MECP2* Gene Variants in Databases

Our modest inventory of five different *MECP2* variants, of which two were derived from NGS data, underscores the need for further harmonization and integration of gene variant information from different sources. Through a simple survey, we have shown that coverage of five selected variants of the *MECP2* gene in the databases under investigation depends upon both their frequency and how long they have been known. This should not be regarded as a criticism of the individual databases for not containing all possible mutations, but rather as an argument for building a better infrastructure for integration of novel genome sequencing data into databases and improvement of interoperability, similar to that offered by the Beacon project in relation to genomic data. This example of limited coverage in a variety of databases illustrates the fact that despite much progress in NGS, genomic and clinical data are still mainly collected and studied in silos by gene or disease, institution or country.

Table 4. Number of database entries for *MECP2* or *RTT* in general and five specific variants (status March 2018).

Database	Total number of <i>MECP2</i> variant entries	Variant 1 c.397C>T missense	Variant 2 c.502C>T nonsense	Variant 3 c.916C>T missense	Variant 4 c.1200_1222del	Variant 5 c.765_1350del
RettBase	4738 (897 unique)	217	363	246	-	-
Korean Mutation Database	35	1	1	1	-	-
ClinVar	1145	1	13	13	-	-
HGMD "professional" ^a	975	-	+	+	-	+
LOVD3.0 <i>MECP2</i>	4588 (807 unique)	197	335	218	-	+
DECIPHER	203	6	4	2	-	-
EVS	117	-	-	-	-	-
ExAC	599	-	-	-	-	-
dbSNP ^{a,b,c}	4229	+	+	+	-	-
dbVAR ^c	469	+	+	+	-	-
EVA	378	+	+	+	-	-

Cafe Variome – dbSNP ^a	500	-		1	1	-	-	-
Cafe Variome – PhenCode	809	1		1	1	-	-	-
Cafe Variome – UniProt	71	1		-	1	-	-	-
Cafe Variome – HGMD ^a	249	-		-	-	-	-	-
Cafe Variome – Locus-specific Databases	10	-		-	1	-	-	-
DisGeNET ^b	+	+		+	+	-	-	-

Number: variant present in this number, + variant present, displayed without details, - variant not found

^adbSNP and the Café Variome request to dbSNP provided different numbers for MECP2 entries, the same applies for LOVD and HGMD. As the Café Variome link uses the public version of HGMD the exact variants are not shown.

^bSearch was done via rs number which does not give the exact variation, only position.

^cThe numbers for dbSNP and dbVAR are from NCBI's Variation Viewer for MECP2 (GRCh37.p13)

Such a finding is consistent with previous observations [39] and others in the Matchmaker Exchange Special Issue (Human Mutation, Special Issue: The Matchmaker Exchange October 2015, Volume 36, Issue 10, Pages i–iii, 915–1019). It can be explained by several factors, including: regulatory data-privacy requirements which inhibit secure data sharing across institutions and countries; poor rewarding of people who collect or make individual contributions to data collection; and the incompatibility of file formats and non-standardized tools and analytical methods (GA4GH, 2016). It is also worth noting that new NGS-derived variants may often be ‘hidden’ in the published literature, for example, within a cohort identified by a broad diagnosis of intellectual disability [22], without specific reference being made (e.g. to RTT and/or *MECP2*) in the title or abstract of an article. As a consequence, many variants may not be picked up by database curators when trawling the literature for new additions. It is neither the intention nor the recommendation of this paper that one database should collect and provide all data but it would be helpful if data could be integrated and findable in such a way that a researcher does not have to search multiple databases to look for one specific variant. In general, adherence to FAIR principles and GA4GH guidelines promise a major improvement.

Need for Better Sharing of Data (Interoperability!) within and between RTT-Relevant Databases

All of the databases tested in this study are accessible by web browser (Graphical User Interface, GUI) but not all of them allow download of search results. The lack of a proper API or download function limits data exchange within different databases which leads to the conclusion that the interoperability of these databases is currently rather poor. Making databases interoperable is of particular value as we found that approaches to several databases may be required in order to locate information about a specific mutation and/or to find all of the available phenotypic information. If these databases were generally able to share and exchange data with each other (as some already do e.g. DisGeNET – ClinVar, RettBase – LOVD), or meta-databases were available to simultaneously approach several databases through a single search function, the search for information would be much easier.

There is a general problem with multiple entries of the same patients or patient groups. Tracing back the submission to the same author/research group can but may not mean that this is the same patient cohort. As we saw in our database survey, the phenotypic data entry varies greatly, such that multiple entries of the same patient would not automatically be recognized as being the same data. Using data about a patient more than once can lead to statistical bias, especially in the field of rare diseases. For this reason, we would encourage the use of registry identifiers (e.g. ID-cards) or privacy preserving record linkage (PPRL).

Patient data laws worldwide do not necessarily forbid uploading genetic and phenotypic data to databases (as long as no personal information is also shared), but medical doctors are not always aware of what is permissible, and may opt to ‘play safe’ by not uploading data at all. Information and training for people who actually produce the data (non-bioinformaticians) would, therefore, be helpful. One such example is that started with the ELIXIR training platform¹⁰, Bring Your Own Data Workshops (BYOD)¹¹ and several other initiatives.

Generally, there is a lack of time and funding to upload and maintain data. Here, we would encourage the community to make mandatory the publishing of datasets alongside the publishing of a research paper, as was started with gene-specific information (see Nucleic Acid Research Instructions to Authors [40]) and continued with raw transcriptomics data (journals require upload on databases like GEO or ArrayExpress before publishing), and also to integrate the data in such a way that one study needs to be uploaded only once and is then findable on other platforms (such as BioStudies¹² [41]). Some positive steps are already being taken in this direction as many European and national grants now require a data management plan for new projects that will allow for sustainability after the project ends.

These problems are not new but were, in fact, flagged up almost 10 years ago when the HVP was initiated [42]. At that time, the late Dick Cotton recognized the need to “collect, curate and make accessible information on all genetic variations affecting human health”, and since then, many additional initiatives have been started. To date, the most active and promising of these is the founding of the Global Alliance for Genomics and Health (GA4GH) in 2013. This offers a similar vision and complementary philosophy and approach, with active Working groups and demonstration projects such as the Matchmaker Exchange and Beacon project.

Another issue relates to the knowledge aggregation sites, repositories and in-house databases which require the owner’s agreement to input or download data from the database or grant permission on a case-by-case basis when the request to access data is part of a specific research project with prior approval from a medical ethical board. Such databases as the US NHS, Rett Database Network, InterRett, AussieRett, and the Dutch Rett Database (Maastricht) are emerging and there is a need to think about ways to connect them. For a start, each entity must make sure that:

1. their database is populated by relevant and useful data (accurate, up to date), which brings with it implications for data maintenance and sustainability;
2. these data are findable and accessible, which may require re-consideration of their access policy; and,
3. their database provides GUI and API infrastructure for connection with others.

¹⁰ <https://www.elixir-europe.org/platforms/training>

¹¹ <https://www.dtls.nl/fair-data/byod/>

¹² <https://www.ebi.ac.uk/biostudies/>

One option could be to use locally installable versions (instances) of genotype-phenotype databases as offered by LOVD, or PhenomeCentral (Phenotips). These in-house databases allow collection of patient data and support (ontology) annotations of genetic and phenotype information. Apart from supporting local data collection, exporting and sharing of (non-patient specific!) meta-data can be made possible in a second step.

The Importance of Being FAIR

In our study we found that, with regard to findability and interoperability of genotype-phenotype databases in particular, there is still much to be done. There are initiatives that work on overcoming this problem. The Beacon project of GA4GH is an initiative that seeks to link molecular data by creating a common searchable infrastructure – the so-called beacons. At the moment about 70 databases/data-sources contribute to this. Currently it is only possible to look for single nucleotide changes – for example, a test search in Beacon for our mutation 1 (X:153296882G>A) yielded 13 hits. The search for small, specific insertions/deletions is currently being implemented but is not yet functional for all databases (personal communication). The RD-connect and Orphanet platforms also provide data – in as much as they link to registries and biobanks, which might have information about the disease. For RTT, the RD-connect catalogue lists three registries: the Italian National Rare Disease Registry, RaDiCo-GenIDA, and the Rett Database Network (none of which provide directly available online genetic and phenotypic data and were not, therefore, included in our survey).

The Importance of Collecting Detailed Phenotypic Information

Among the genetic variants of *MECP2*, there are those that cause RTT, those that cause mild intellectual disability, and there are neutral/benign variants. Among the disease-causing forms, there are severe and mild variants of typical/classical RTT and atypical RTT e.g. preserved speech variant [20]. An underlying minimal set of core and supporting criteria must be fulfilled in order for a clinical diagnosis of RTT to be given [43]. Despite this, however, both classical and atypical forms display a broad range of phenotypes. To name but a few of the characteristics of the syndrome, some individuals with RTT cannot walk while many do, and most develop scoliosis or epilepsy but not all. Among those with epilepsy, there is no single anti-epileptic treatment that works for all, indicating for example, different physiological roots, although practice preferences and availability of specific agents may also affect the choice of medications. Mood and character of individuals vary greatly, too. It is clear that RTT is a complex syndrome with multiple factors – including levels of X-inactivation, genomic, epigenetic and other environment influences – affecting its phenotypic presentation. Currently, there are several approaches to capture the phenotype realized in the databases we investigated:

1. By diagnosis: RTT- or disease-specific databases especially, give the information that the carrier of this *MECP2* mutation has been diagnosed with RTT (or others) (RettBase, ClinVar, Café Variome/PhenCode, DisGeNET, HGMD). In some cases, the diagnosis is even linked to an identifier (OMIM, MeSH, DOID).
2. A detailed description of the phenotype is given – but without diagnosis (DECIPHER, HGMD).
3. The effect of the genetic variation is given as measured/observed or predicted (e.g. using PolyPhen2) molecular biological consequences (LOVD, ExAC, dbSNP) or phenotype ‘damaging’ effect (EVS).

To cover the richness of medical observation we strongly encourage the collection of detailed phenotype descriptions of genetic variations. One way to contribute to a more detailed elucidation of phenotypes is through encouraging a clearer use of terms which should include the use of ontologies, identifiers and minimal information standards [44]. In this respect, the application of HPO terms is widely advocated within the rare disease field/community, as illustrated by the GA4GH recommendation on this topic¹³. This is where population-based/epidemiological studies such as the US NHS and AussieRett, both of which track and record the longitudinal natural history of RTT, could make a major contribution in the future.

Finally, we would like to stress two things. Firstly, we recognize that any work such as we are recommending to further develop, maintain and integrate existing databases does not come without costs attached. However, we believe that each of the databases we have investigated in this study is of value and should be well-supported and well-funded in order to maximize use of the data and yield maximum long-term benefits. Secondly, we recognize that diseases are rarely truly monogenic. All genes function in an environment of other gene products, including their variations (epistasis). In addition to classic examples, such as PKU [45] and Cystic Fibrosis [46], this was recently illustrated in the cancer field with the added value of gene expression data to established oncogenic driver mutations [47]. A similar argument was put forward by McArthur and colleagues when they advocated for the inclusion of RNA-seq to increase the diagnostic yield within the field of rare diseases [48]. This phenomenon may also be translated to RTT with *MECP2* mutations as major ‘drivers’. To read and interpret a disease-causing variant within the individual’s genetic environment will be one of the major challenges in the future.

¹³ <https://genomicsandhealth.org/working-groups/our-work/phenotype-ontologies>

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Part Two

Applied Research Relating to the
Communication Challenges,
Needs and Potential
of Individuals with Rett Syndrome

Chapter 5

Cognition, Communication and Behavior in Individuals with Rett Syndrome

Published as:

Townend, G.S., Kaufmann, W.E., Marschik, P.B., Fabio, R.A., Sigafoos, J., & Curfs, L.M.G. (2017). Cognition, Communication and Behavior in Individuals with Rett Syndrome. In W.E. Kaufmann (Ed.), *Rett Syndrome* (1st ed., pp. 50-61). London: Mac Keith Press.

Introduction

One of the main criteria for clinical diagnosis of Rett syndrome (RTT), as defined by Neul et al. [1] is that of “partial or complete loss of acquired spoken language” (p.946). For many parents the communication difficulties experienced by their child (at any age) are one of the greatest challenges – and one of the greatest frustrations – they face. Questions of how an individual understands and interacts with the world, how they can best be helped to express themselves, how they can be educated and enabled to participate in society in a meaningful way are of fundamental importance and are grounded in the phenomenologically overlapping areas of cognition, behavior and communication.

In this chapter we will review the research to date and the current levels of knowledge and thinking with regard to cognition, communication and behavior in individuals with RTT, including early development, later skills and deficits and strategies for intervention and management.

Cognition

Relatively few studies to date have formally investigated information processing and learning abilities of individuals with RTT. By and large, this has been due to a lack of appropriate testing mechanisms and the difficulty of applying common or standardized instruments for the measurement of cognitive abilities in individuals with RTT. Traditionally, studies fall into two categories. The first assesses cognition directly (e.g. the Bayley Scales of Infant Development [2]) through verbal responses or manipulation tasks that require good hand control to demonstrate the development of concepts such as object permanence and means-end (cause and effect) as precursors to intentionality. The second assesses adaptive behaviors through parental/caregiver interviews and checklists (e.g. the Vineland Adaptive Behavioral Scale [3]). Early literature, utilizing such assessments, has tended to place individuals with RTT at a developmental age of between 1 and 18 months. A review published by Demeter [4] at the turn of the century provides a useful synthesis of studies up to that date, pointing out the shortcomings of classical developmental tests when applied to individuals with RTT. “If we define intelligence as the capacity to process information, we see, for instance, that the Bayley mental scales, the Uzgiris and Hunt scales and other diagnostic instruments only assess this capacity for a part of the (RTT) girls' world, a part they have showed a selective difficulty to handle efficiently. Therefore, we have to look to the interests of these girls, and use them to get a more complete image of their information processing capacity.” [4, p.230].

Demeter offers an alternative approach to testing based upon a parental questionnaire that recognizes differences in the types of stimuli that are of most relevance to individuals with RTT, is sensitive to the idiosyncratic and subtle ways in which individuals demonstrate learning, and accommodates fluctuations in cognitive performance and communication

across time and place. More than a decade later, a review by Byiers and Symons [5] suggests that a gap in practice still exists between knowing what form of assessment is desirable and what is available. Their review of 27 studies assessing intellectual and adaptive functioning of individuals with RTT is the most comprehensive to date and includes studies based on published and unpublished protocols, as well as estimates according to clinical judgement. In particular, they consider the appropriateness of the assessment tools utilized in the reviewed studies and conclude that “developmental estimates for individuals with RTT based on sensorimotor assessments should be viewed with skepticism” [5, p.163] and “results of traditional cognitive assessments with individuals with RTT should not be over-interpreted” [5, p.164].

Given that dys-/apraxia, or “partial or complete loss of purposeful hand skills” [1, p.946], is another of the main clinical features of RTT, accompanied by stereotypical hand movements, it is unsurprising that traditional tests relying on object manipulation are now recognized as inappropriate and their results called into question. In 2006, Baptista and colleagues [6] published a study that pointed to the potential benefits of using ‘new’ eye gaze technologies to assess cognitive development more accurately. They showed, in a rudimentary way, through measurements of visual fixation, that individuals with RTT were capable of intentional eye gaze. Since then there has been increasing exploration of eye gaze/eye tracking technology to measure a range of cognitive processes in individuals with RTT. These forms of assessment recognize the importance of the “intense eye communication – eye pointing” [1, p.946], which is reported in almost all individuals with RTT. Of particular note are studies by research teams at Montefiore Medical Centre in New York [7-11], Mackenzie Presbyterian University in São Paulo [12, 13] and Boston Children’s Hospital [14]. Results to date have been mixed. Those studies which focus on measures of non-verbal cognition and visual preference/visual fixation verify a preference for social stimuli among individuals with RTT and suggest that eye gaze in RTT is intentional, thereby concluding that eye tracking technology can be used to study elements of cognition in this disorder. When using eye tracking to test attention and recognition memory (for both faces and patterns), Rose and colleagues [10], however, found that the performance of individuals with RTT was significantly poorer than their typically developing peers. When using eye tracking to test concept recognition, Velloso and colleagues [13] had also concluded that individuals with RTT were unable to demonstrate reliable recognition of concepts of color, shape, size and position to verbal command. A recent psychometric validation of a modified version of the Mullen Scales of Early Learning (MSEL) for individuals with RTT, which includes an eye-tracking component, confirmed average lower performance across developmental domains [14]. However, it also demonstrated that some individuals have age- or above age-adequate abilities in the receptive language and visual reception (non-verbal) domains. This goes further than previous studies of adaptive behavior [15-17] in showing that, within the context of the aforementioned limitations, developmental skills measured by the MSEL can provide an overall assessment of cognition

in RTT.

A number of studies have explored factors, such as hand stereotypies, which may influence attention in individuals with RTT [18-20], and suggest that if the stereotypic behaviors are prevented, for example by embracing the individual or by restraining their hand, their attention to stimuli may improve. Fabio and colleagues [21], along with other researchers, have explored associations between a broader range of cognitive, sensory and neurophysiological features. For example, Vignoli and colleagues [15] combined the use of EEG, eye tracking and behavioral measures to examine links between epilepsy and cognition, whilst Stauder et al. [22] and, more recently, Peters et al. [23] considered links between auditory responses and (cortical) information processing. The Vignoli study [15] showed that the later the onset of seizures the greater the ability to respond to verbal commands, but that as seizure frequencies increase the ability to respond decreases. They also demonstrated that as EEG abnormalities become more pronounced, cognitive performance, as marked by the ability to recognize and respond to instructions, decreases. The Stauder study [22] tested visual and auditory event-related potentials, the results of which suggested slower information processing and reduced brain activation in a cohort of individuals with RTT compared with a control group. In the Peters study [23] measurement of gamma-band oscillatory responses during a passive voice discrimination test showed a decreased response to a familiar voice in individuals with RTT compared with individuals with *MECP2* duplication. This is tentatively interpreted as being indicative of greater social impairment in individuals with RTT. As the numbers in the study are small, however, Peters and colleagues recommend further testing in this area. Furthermore, they suggest that because “this paradigm did not require any motor abilities or hand use, it can be more suitable as a measure of cognitive processing assessing recognition and discrimination as well as processing of socially relevant stimuli as compared to conventional behavioral/psychological measurements” [23, p. 150].

Such conclusions, pointing to limitations in cognitive capacity, seem to be at odds with the anecdotal evidence of many parents who report that their child is far more cognitively able than can be demonstrated on assessment or is suggested by current research. This mismatch may be answered, at least in part, by the apraxia which limits the ability to respond easily on command, meaning that it is not simply a matter of changing the access method for assessment of skills, but also the manner and style of presentation. At the current time, therefore, it can be concluded that although eye gaze and eye tracking technologies appear to offer the most appropriate access to assessments of cognition, there is still some way to go in order to develop robust assessments that can accurately capture the skills and abilities of individuals with RTT and that can be validated and set to appropriate norms [24].

Communication

Communication Skills

Individuals with RTT demonstrate severe limitations in their ability to communicate through conventional channels, such as hand signs/gestures and speech [25, 26] which, according to the core clinical criteria [1], is due to a regression or loss of previous acquired skills and subsequent impairment in acquiring new ones. This is supported by findings from parental interviews and questionnaire administration using population-based and international samples [27, 28], which reveal that the level of expressive language acquisition is in general low, but to some extent influenced by genotype. In one study involving 542 individuals with classic RTT and 96 with atypical RTT enrolled in the US-based Natural History Study, 77% of those with classic RTT were reported to have acquired single words, but only 18% phrases. Of those with atypical RTT, 94% of individuals classified as ‘atypical better’ acquired single words and 54% phrases, whilst only 36% of those classified as ‘atypical poorer’ acquired single words and 6.7% phrases [29]. Analysis of early communicative behaviors through the application of retrospective video-analysis and/or parental interviews or questionnaires, which probe the pre-diagnosis period [30-39], has shed further light on early development. This has demonstrated that in many cases development in the first year of life is not as asymptomatic as previously thought and deviations from typical development can be identified prior to, as well as after, the onset of regression. For example, with a reduction in gestural and vocal repertoire, abnormal quality of (ingressive) vocalizations, failure to reach milestones such as canonical babbling and deficits in socio-communicative behaviors (joint attention and reciprocity).

The lack of ability to communicate is recognised as being due, at least in part, to the influence of apraxia (an inability to control purposeful, voluntary movements) [9], although the extent to which this, as opposed to deeper language and/or cognitive impairments are to blame, is a subject for ongoing debate. A number of studies have sought to probe deeper into the communicative behaviors of individuals with RTT, to explore levels of underlying intentionality and the range of functions, as well as the means by which they are able to express themselves. Sigafos et al. [40] offer a systematic review of eight studies that were conducted prior to 2006, whilst later studies [41-45] have either collected parental reports through questionnaires and structured interviews, or applied behavioral or observational checklists (such as the Inventory of Potential Communicative Acts (IPCA) [46]) and/or experimental paradigms. In general, their findings suggest that the majority of individuals with RTT operate at pre-linguistic, pre-intentional levels of communication, with their behaviors interpreted by caregivers and communication partners as ‘potential communicative acts’ [47]. Behaviors may include the use of stereotyped hand movements, facial expressions, body movements, undifferentiated vocalizations, and hyperventilation, with eye gaze reported as the most frequent form of expressive communication behavior

across the studies. Some authors have suggested that the eye gaze may be limited to fixating on an object, indicating need or preference at a pre-intentional level and they question whether individuals with RTT can use truly referential eye gaze, demonstrating communicative intent by switching gaze between a desired object and a partner [25, 43]. Hetzroni & Rubin [41], however, have demonstrated that this behavior can be trained in individuals with RTT and, more recently, Urbanowicz and colleagues have shown that eye gaze can be used effectively by some individuals with RTT to make choices and requests [26, 48]. The functions attributed to communication behaviors are commonly acknowledged as being to seek attention, to protest, to request and/or to make choices. At the present time there is little published literature that demonstrates the use of higher level communication skills, although there is much anecdotal evidence shared between parents and professionals, for example through Facebook posts.

Several of the afore-mentioned studies also point to apparently low levels of receptive language, especially when standardized tests are employed. The limitations of such tests have already been discussed and, in studies where parents have been interviewed, they frequently express the view that their children know more than they are able to express or to demonstrate on assessment [43, 45] leading once more to calls for the development of more objective (eye tracking-based) language assessments, which can be used to validate data gathered from parental reports. Alongside these studies, research profiling genotype-phenotype relationships also delineate more specific speech-language profiles according to both variant and *MECP2* mutation type [27, 49-51]. In particular, those who are diagnosed with 'milder' mutations such as P.Arg133Cys (often associated with the so-called preserved speech variant, PSV), present with a somewhat milder phenotype, being likely to develop more words pre-regression and retaining or regaining an ability to speak and using single words or simple sentences post-regression, as well as retaining or regaining more control over hand function and an ability to walk [27, 29, 52, 53].

Communication Intervention and Management

Intervention studies employing the use of augmentative and alternative communication (AAC) to improve the communication skills of individuals with RTT are increasingly being reported in the published literature. A systematic review conducted by Sigafoos and colleagues [54] identified nine small studies (with a total of 31 participants) in which various forms of AAC had been introduced, including the use of gestures, picture symbol boards and computers with speech output/speech generating devices (SGDs). The authors found broadly positive outcomes related to the use of AAC for individuals with RTT; however, they cautioned that the existing corpus of studies was relatively small-scale and few in number (n=9 studies with a total of 31 participants) and hampered by methodological limitations, such that the benefits of these studies could not be pronounced conclusive.

Since that time further studies have, in various ways, reported on the application of AAC to individuals with RTT. Surveys of speech-language pathologists (SLPs) and parents, for example those conducted by Wandin et al. in Sweden [55] and Townend et al. in the Netherlands [56], have highlighted a range of AAC systems and strategies that are utilized by SLPs working with individuals with RTT. These include the use of pictures/objects of reference, communication charts and books, single- and multi-message SGDs, and communication apps. Many of these AAC systems are based on the use of picture symbols and may be accessed through direct touch or, increasingly, through eye gaze/eye tracking technology. AAC, in general, is reported by SLPs and parents to have a positive effect on the communication of individuals with RTT, especially at the levels of choice making and requesting, which are the most frequent goals for intervention, as reported by Wandin et al. [55]. At the level of experimental design studies, more recent publications have also supported this view. Studies by Byiers et al. [57], Stasolla et al. [58, 59] and Simacek et al. [60] have aimed to teach requesting and/or choosing behaviors through the use of a voice-output micro-switch or SGD, or through the manual exchange of picture symbols. As with the earlier studies reviewed by Sigafoos et al. [54], the numbers across the four studies are small (a combined total of 11 participants), yet the results are promising, at least in relation to the development of requesting and choice-making behaviors.

Interest in eye gaze technology as a form of access, both in relation to assessment of cognitive and comprehension skills (as described above), and as a medium for intervention, has grown in the last several years. With increasing recognition of the influence of apraxia on the communication behaviors of individuals with RTT, eye gaze is acknowledged by many to be the most appropriate and reliable access method and intervention studies utilizing eye gaze/eye tracking technology are emerging. The above-mentioned modification of the Mullen Scales of Early Learning (MSEL) [14] includes two independent but complementary versions, the first consisting of adaptations on response timing and size and motivation-level of objects, the second completely eye tracking-based. Although promising, the latter measure highlights the limitation of this technology, since it is restricted to assessing receptive language and visual function. At the present time, differences in opinion and practice exist in relation to goals for intervention. There is a gap between the published studies (as reported above), where materials and options are limited to small numbers of choices, and interventions reported anecdotally where individuals with RTT are introduced to broad-based 'robust vocabularies' in the form of complex communication books or dynamic screen SGDs. In the latter scenario, the expectation is that individuals with RTT can achieve if given the right access to communication and through this can access education and participation in society. It is hoped that in the near future more studies will be published in this area so that a stronger body of evidence can be formed in relation to the use and benefits of AAC for individuals with RTT.

Additional areas for intervention, which are increasingly reported in relation to individuals with RTT, include developing reading and writing skills [61] and providing training in partner communication strategies [55, 62]. The beneficial effects of music and music therapy on stimulating interaction and communication between individuals with RTT and their caregivers have also long been acknowledged [63-65].

Behavior

Although the diagnostic criteria for RTT primarily focus on communicative and motor features, behavioral abnormalities are also prominent. As reported by a recent study by Cianfaglioni et al. [66], who examined a group of 91 adults and children with RTT utilizing the 'Rett Syndrome Behaviour Questionnaire' (RSBQ) [67] and compared them with a cohort of individuals with six other syndromes associated with intellectual disability, the range of behavioral abnormalities is wide. Cianfaglioni et al. [66] found that hand stereotypies, breathing irregularities, night-time unrest, anxiety or inappropriate fear, and low or changeable mood were commonly reported in the RTT group. Self-injury was lower but, where reported, it was found to be related to over-activity and impulsivity, two features associated with milder forms of RTT and recognized predictors of self-injury in other syndromes and autism spectrum disorders [68, 69]. Whilst there were some differences in the weighting of behaviors between this and previously conducted studies [67, 70], that may be accounted for by the fact that previous studies reported on predominant child samples whilst Cianfaglioni's cohort included both adults and children. One particularly significant feature compared to the contrast group in this study was the type of hand stereotypy observed in individuals with RTT, notably that of hand wringing. Hand stereotypies such as hand flapping may be found in other forms of intellectual disability, yet hand wringing appears to be unique to RTT and, according to Robertson et al. [70] is especially evident in individuals with an p.Arg255X or p.Arg270X mutation but less likely in those with a p.Arg294X mutation.

The early focus on autistic behavior, which was included in the seminal publication by Hagberg and colleagues [71], is a result of the impairment in communication, social withdrawal, and severe stereotypies that are observed during the regressive phase of RTT. Most subsequent studies have emphasized the transient nature of these autistic features and their prominence in the context of a milder phenotype (i.e. better ambulation and hand use) [72]. A study by Kaufmann et al. [17], however, found that although mild autistic behavior persisted beyond regression it was relatively independent of overall clinical severity. Kaufmann and colleagues suggest that differences in identification of autism may be due to methodological differences and argue for further research into the RTT phenotype utilizing "more comprehensive cognitive and behavioral batteries, and examining their associations with physiological and/or neurological data (e.g. neuroimaging, electroencephalogram)" [17, p.245]. A similar argument is presented in

another study by the same group. Barnes et al. [16] describe the first attempt to systematically examine anxiety-like behaviors in individuals with RTT using standardized assessment tools. This is an important area for evaluation as anxiety is commonly reported [66, 73, 74], with fear/anxiety behaviors most frequently seen among individuals with p.Arg133Cys and p.Arg306Cys mutations [70]. Correct identification of behaviors, and the mechanisms and functions underpinning them, in individuals who by virtue of their communication difficulties cannot easily draw attention to how they feel or how they perceive the world, carries implications for management and therapeutic intervention and must, therefore, be taken seriously.

Treatment of Behavior

Behavioral intervention strategies have been used for the management of a variety of manifestations in RTT, including sleep dysfunction [75], feeding skills [76], and cognitive and communication skills [21, 57, 61]. As for other areas covered by this chapter, these studies include small series of participants with a wide age range and different methodologies. Use of applied behavioral analysis has only been either theorized [77] or anecdotally reported (reviewed by Lotan [78]). When behavioral interventions or music therapy are not employed or are considered ineffective, psychopharmacology can be the treatment of choice for anxiety-like and disruptive behaviors. Again, virtually no publications are available in this area and the use of selective serotonin reuptake inhibitors (SSRIs) for anxiety is mentioned in a few reviews focused on novel drug interventions [79, 80]. The recently reported mild improvements in social avoidance in an open label trial with insulin-like growth factor (IGF-1) are encouraging, but they should be taken with caution [81].

Conclusion

We have come a long way in our understanding of RTT in the 50 years since Andreas Rett (see [82] for a translation into English) first described the cluster of symptoms that later came to be known as RTT. Our knowledge and understanding of the phenotypic presentations and their underlying genetics has moved on considerably since the discovery of the *MECP2* gene in 1999 and we are now gaining new insights into the biological pathways influenced by *MECP2* [83, 84]. We have begun to separate out aspects of communication and behavior according to mutation, but we still have much further to go to fit together all the pieces of the jigsaw. Cognition, communication, and behavior are not simply a matter of genetics, but are the result of a complex interaction within and between each individual, the people around them, their environment, and the supportive strategies and tools that are offered them. We recognize the influence of apraxia on the ability of individuals to respond to command, for example, and to execute actions under voluntary

control, and we recognize the effect of other neurophysiological, sensory and behavioral elements on communication and cognition. More specific tools need to be developed to evaluate the cognitive and communicative abilities, as well as abnormal behaviors, of individuals with RTT appropriately and accurately. Well-conducted assessments should underpin the formulation of appropriate goals that acknowledge the potential of the individual and offer appropriate support through the use of AAC, including but not limited to eye gaze and eye tracking technology. Furthermore, advances in the development of behavioral interventions and/or neurobiologically-based drug treatments offer potential avenues for future exploration.

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Chapter 6

Comparing Social Reciprocity in Preserved Speech Variant and Typical Rett Syndrome During the Early Years of Life

Published as:

Townend, G.S., Bartl-Pokorny, K.D., Sigafos, J., Curfs, L.M.G, Bolte, S., Poustka, L., Einspieler, C., & Marschik, P.B. (2015). Comparing social reciprocity in preserved speech variant and typical Rett syndrome during the early years of life. *Research in Developmental Disabilities*, 43-44, 80-86. doi:10.1016/j.ridd.2015.06.008

Abstract

This study compared early markers of social reciprocity in children with typical Rett syndrome (RTT) and in those with the preserved speech variant (PSV) of RTT. Retrospective video analysis of 10 toddlers with typical RTT and five with PSV investigated participants' orientation to their name being called between the ages of 5 and 24 months, prior to their diagnosis. From analysis of the recordings two distinct profiles were apparent. Although response rate was higher in girls with typical RTT than PSV at 5 to 8 months this noticeably reversed from 9 to 12 months onwards. By two years of age there was a markedly higher rate and range of responses from girls with PSV. This study contributes to the delineation of different profiles for the variants of RTT.

Keywords

Rett syndrome; Preserved speech variant; Family videos; Home videos; Response to name; Retrospective video analysis; Social awareness.

Introduction

Rett syndrome (RTT) is a neurodevelopmental disorder of genetic origin, typically characterized by seemingly-normal development in the first year of life followed by a regression in and loss of skills. Individuals with RTT have previously been considered to be profoundly intellectually as well as communicatively impaired and to demonstrate autistic spectrum-like behaviors, in addition to displaying stereotyped hand movements and a loss in purposeful hand use [1-11]. A number of variants of RTT have been identified which, following confirmation of a diagnosis of RTT through genetic analysis, can be distinguished from each other according to certain clinical criteria [6, 12]. In recent years, understanding more precisely the relationships between, and defining characteristics of, a genotype-phenotype match for both mutation type and variants of RTT has become an increasing focus for research [e.g., 13-17]. In addition to classic or typical RTT, the milder 'Zappella' or preserved speech variant (PSV) [18, 19] is one of the more studied variants, although the existing pool of knowledge regarding RTT, its variants and their characteristics pre- and post-diagnosis and pre- and post-regression is still relatively small.

A number of researchers have sought to fill the knowledge gap either by interviewing parents to elicit information about the early and current (pre- and post-regression) development of their child's communication skills [20] or by exploring the early (pre-diagnostic) development of children with RTT through the medium of retrospective video analysis. These retrospective studies have included both consideration of early general development [21-23] and socio-communicative/speech and language development in children with typical RTT [24] and children with PSV [25-29]. Other studies that we have conducted have also compared typical RTT and PSV [30] and have drawn a comparison between typical RTT, PSV and a typically developing toddler [31]. What each of these studies has so far demonstrated is that the early development of children with RTT is not as asymptomatic as originally assumed and that deviations from typical development can be identified prior to the onset of regression.

One domain of socio-communicative development not explored in these retrospective analyses is that of social reciprocity in children with RTT. This area has been studied extensively, however, in relation to early identification of autism spectrum disorder (ASD) and other forms of developmental disability. Social reciprocity, or rather the lack of it, during the first two years of life has been demonstrated to be a significant indicator of a later diagnosis of ASD and/or developmental disorders [11, 32-38]. In particular, observing the child's response to their name being called has been found to be a good marker of social reciprocity or social awareness. Studies have shown that infants as young as 4.5 to 5 months of age are able to demonstrate early signs of recognizing the sound pattern of their own name, both through employing modified head-turn preference tests [39] and through the use of near-infrared spectroscopy [40]. These experiments do not suggest, however, that children of such a young age are yet able to imbue the name call with communicative

intent, to recognize the ostensive signal. The ability to mentalize is thought not to develop until around 18 months of age [41]. Indeed, different areas of the brain were triggered in the infants of 5 months old when responding to their name as opposed to adults reacting to their own name, in whom the area associated with mentalizing was found to be triggered [42]. Nevertheless, at only 4.5 to 5 months old typically developing infants are at least able to recognize their own name as a personally-significant sound pattern and to react. The failure to respond to one's own name or to require more prompts before responding have both been found, through retrospective video analysis studies, to be significant and reliable early predictors of a later diagnosis of autism, and to distinguish autism from other forms of developmental delay and typically developing children between about 8 months to two years of age. Usually this is suggested to be in combination with other markers such as lack of eye contact rather than as a single factor [32-38]. This same lack of response to name was also found to be significant by 12 months of age (though not at 6 months) in two prospective studies of infants at risk of ASD [43, 44].

The debate surrounding the similarities and differences between ASD and RTT and its variants has, in recent years, begun to be explored at two levels: one pertaining to the 'outer' observable, behavioral features of the conditions (the phenotypic representation) [45] and one relating to the 'inner' biological, genetic or epigenetic influences on brain structure and development (the genotypic representation) [46]. Trevarthen and Daniel [11] attempt to draw these two together. They liken the 'outer' behaviors witnessed during the regression stage of RTT to features of ASD, namely the reduction in interest in people accompanied by the apparently reduced communicative intent, difficulties in shared attention and changes in motor coordination. However, they go on to acknowledge that the renewed sociability and emotional sensitivity which emerge in the third stage of RTT set the two conditions apart, concluding that there is a different underlying 'inner' basis: "Notwithstanding that the two conditions show clear differences in both brain growth and early development of skills and sociability, the first signs of autism and Rett syndrome have important similarities" [11, S25].

In the current study we focused on questions relating to early social awareness (social reciprocity) and RTT as a contribution to the growing body of knowledge and understanding about the characteristics of RTT and its variants, both before and during the regression phase. The aims of our descriptive study were three-fold:

- (a) To explore whether individuals with RTT demonstrate social awareness (social reciprocity) during the early years of life;
- (b) To determine whether there are changes over time which may span the pre- and post-regression period;
- (c) To ascertain whether there are differences in these social markers between typical RTT and PSV.

Method

Building on the methodological footsteps of many of the social reciprocity in autism studies as well as on our own previous work [24-31, 47], we utilized retrospective video analysis as a way of observing behavioral responses to name as a marker of social reciprocity in girls with typical RTT and PSV between the ages of 5 and 24 months.

Participants

Fifteen girls with a confirmed genetic diagnosis of RTT were recruited for this study. All had uneventful pregnancy and birth histories, and were singleton births with birth weight, length, occipitofrontal circumference and Apgar scores all within normal limits. According to the genetic testing, the girls were all *MECP2* positive. Ten girls met the clinical criteria for typical RTT and five met the criteria for PSV [6]. Although the girls were of differing ages at the time of the study, retrospective video analysis focused on the participants when they were aged between 5 and 24 months of age, prior to diagnosis.

Ethical Approval

The study was approved by the local research ethics committee and the parents gave informed consent to participation in the study and to the publication of the results.

Procedure

The procedure was similar to that reported in a previous study [31] that compared the two variants of Rett syndrome. It also followed the retrospective video analysis procedures we previously employed to explore aspects of early socio-communicative development in both typical RTT [24] and PSV [27]. Video recordings had been made by parents during the course of typical daily activities as well as on special occasions (e.g. birthday parties), at a time when they had been unaware of their daughter's diagnosis of RTT. In total 2042 minutes of recorded footage was available for analysis across all participants. The videos were divided into four distinct age categories: 5 to 8 months (median 46 minutes), 9 to 12 months (median 77 minutes), 13 to 18 months (median 93 minutes), and 19 to 24 months (median 100 minutes). For the purposes of this study, the child's behavioral response to hearing her name being called was of interest as a marker of social reciprocity. Analysis and coding of the whole footage was conducted by three members of the team (KDB, CE, PBM) with support from the Noldus Observer-XT tool. Where any disagreement arose between the coders (7% of behaviors), the sequences were discussed within the team and a consensus was agreed.

Three categories of behavior (the dependent variables) were coded according to the following operational definitions (please see also key to Fig. 2):

- (a) “Eyes and/or head”: the girl looks to the person who calls her name, i.e. she turns her head towards the person and/or moves her eyes to make eye contact with that person; eye contact is not accompanied by verbal behaviors or gestures; a positive coding may also include looking to the camera if the person holding the camera calls the child’s name;
- (b) “Eyes and/or head and verbal” corresponds to any verbal behavior (e.g. (proto)word, unspecified vocalization) in addition to making eye contact; and
- (c) “Eyes and/or head and gestures” refers to any gesture (e.g. waving to greet) in addition to making eye contact.

Results

Table 1 shows how often each participant’s name was called and a response could be expected compared with how often they reacted during each time interval. It also illustrates how often no coding could be assigned due to there being no instances of the child’s name being called during the video clips or no video being available for a particular child during a given time period. In all but two instances it can be seen that for all participants at all time intervals the number of responses actually observed was lower than the number expected. This appears to be irrespective of age or RTT variant. Further descriptive detail is illustrated in Table 2 and Figs. 1 and 2.

Table 2 adds detail to show how the overall response rate for each of the two groups was calculated during each time interval whilst Fig. 1 illustrates the changes in response rate over time more clearly as a comparison between the typical RTT and PSV groups.

Fig. 2 illustrates graphically the modes of behavioral response(s) observed by group and time period.

The results indicate that the response rate was initially higher in girls with typical RTT than PSV, at 5 to 8 months, but that this was reversed from 9 to 12 months onwards. At 13 to 18 months there was a noticeably higher response rate from girls with PSV compared with typical RTT and this differential was maintained at two years of age with a markedly higher rate and range of responses from girls with PSV. The majority of responses involved eye contact and/or turning of the head, which remained at a reasonably consistent level throughout in the PSV group but dropped off in the typical RTT group. The girls with typical RTT used some vocalization to accompany their responses at a low level throughout although no accompanying gestures were observed in this group at any age. In contrast the girls with PSV only added accompanying vocalizations and gestures to their eye contact and/or turning of the head movements in the final time period, by age two years. Verbal behaviors and gestures were never observed together as a response to name in either group and, therefore, were not included as a coding option.

Table 1. A comparison of the expected versus observed reactions to name being called, in girls with preserved speech variant and typical Rett syndrome between the ages of 5 and 24 months.

Child	5-8 months			9-12 months			13-18 months			19-24 months		
	Reaction expected	Reaction observed	Reaction expected	Reaction observed	Reaction expected	Reaction observed	Reaction expected	Reaction observed	Reaction expected	Reaction observed	Reaction expected	Reaction observed
RTT 1	0	0	0	0	1	1	1	1	n/v	n/v	n/v	n/v
RTT 2	6	3	0	0	n/v	0	n/v	n/v	1	0	0	0
RTT 3	12	3	n/v	n/v	n/v	n/v	n/v	n/v	n/v	n/v	n/v	n/v
RTT 4	5	2	4	0	n/v	0	n/v	n/v	n/v	n/v	n/v	n/v
RTT 5	11	5	4	1	26	1	8	8	20	2	2	2
RTT 6	4	1	0	0	n/v	0	n/v	n/v	1	0	0	0
RTT 7	3	2	4	4	n/v	4	n/v	n/v	n/v	n/v	n/v	n/v
RTT 8	1	0	15	5	8	5	0	0	5	0	0	0
RTT 9	n/v	n/v	1	0	12	0	1	1	1	0	0	0
RTT 10	n/v	n/v	11	0	10	0	0	0	4	2	2	2
PSV 1	5	2	15	5	9	5	4	4	15	6	6	6
PSV 2	32	8	28	10	7	10	3	3	n/v	n/v	n/v	n/v
PSV 3	n/v	n/v	n/v	n/v	5	n/v	1	1	6	5	5	5
PSV 4	n/v	n/v	0	0	3	0	1	1	3	0	0	0
PSV 5	n/v	n/v	n/v	n/v	7	n/v	6	6	24	9	9	9

Reaction expected = occasions when participant's name was called and a response could be expected.

Reaction observed = participant's response according to defined behaviors.

n/v = no video available.

Table 2. Comparative data collection from retrospective video analysis of the responses to name being called in girls with preserved speech variant and typical Rett syndrome between 5 and 24 months of age.

Age (months)	Number of cases		Number of calls		Reaction not possible		Reaction expected		Reaction observed		No reaction		Response rate (%)		Total recording time (min)	
	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV
5-8	8	2	57	40	15	3	42	37	16	10	26	27	38.10	27.03	356	46
9-12	9	3	51	53	12	10	39	43	10	15	29	28	25.64	34.88	512	77
13-18	5	5	67	33	10	2	57	31	10	15	47	16	17.54	48.39	590	93
19-24	6	4	37	52	5	4	32	48	4	20	28	28	12.50	42.55	268	100

Number of cases = number of participants for whom video recordings were available during the defined age period, out of the total number of 15 participants.

Number of calls = total number of times that the collective participants' names were called in the video recordings for the defined age period.

Reaction not possible = total number of times that the collective participants' responses to their names being called could not be included, for example, when they were already looking at the person who called their name.

Reaction observed = total number of times that the collective participants responded according to one of the defined behaviors.

Reaction expected = total number of times that the collective participants' names were called minus the times that a reaction was not possible.

No reaction = total number of times that a reaction was expected but no behavioral response was observed.

Response rate = percentage of reactions observed in relation to reactions expected.

Figure 1. Changes in response rates of girls later diagnosed with typical Rett syndrome and the preserved speech variant to their name being called (reaction observed as a percentage of reaction expected), between 5 and 24 months of age.

Figure 2. A comparison between the behavioral responses of girls later diagnosed with typical Rett syndrome and the preserved speech variant to their name being called, between the ages of 5 and 24 months.

Eyes and/or head = the girl looks to the person who calls her name, i.e. she turns her head towards the person and/or moves her eyes to make eye contact with that person; eye contact is not accompanied by verbal behaviors or gestures. A positive coding may also include looking to the camera if the person holding the camera calls the child's name.

Eyes and/or head and verbal = any verbal behavior (e.g. (proto)word, unspecified vocalization) in addition to making eye contact.

Eyes and/or head and gestures = any gesture (e.g. waving to greet) in addition to making eye contact.

Discussion

The aims of our study – to explore whether individuals with RTT demonstrate social awareness during their early (pre-regression) years, whether there are changes that span the regression period, and whether there are different profiles for typical RTT and PSV, were grounded in the knowledge we have to date of the characteristics of RTT. One of the most prominent features of RTT is the four-stage pattern of stagnation and regression [4,

6], with stagnation in development beginning any time between 6 and 18 months of age in typical RTT and regression of acquired skills between the ages of one and four years. This period of regression has been noted to include a reduction in interest in people and objects even though eye contact may be maintained [9]. Following regression there is typically a so-called pseudo-stationary period during which there may be renewed interest in people and some development in communication skills [e.g., 11], particularly through the use of eye gaze. PSV is characterized by a milder presentation with, amongst other things, better verbal skills and a somewhat later onset of regression, reported to be from around two to four years of age [18, 19, 26]. The results of the current study could, therefore, be considered to be completely in line with these patterns as the response behaviors of the typical group peaked during the first period from 5-8 months and thereafter tailed off, indicating a stagnation then reduction in skill and/or interest. The PSV group's increased frequency of responses after the initial time block, with a peak at 18 months and relatively little tailing off by the age of two in comparison with the typical RTT group also concurs. The fact that the participants with PSV also demonstrated an increase in modalities at age two, which was not mirrored by the girls with typical RTT, may also be significant. However, without more in-depth qualitative analysis of the type of vocalizations and further observation beyond the age of two and into the post-regression/pseudo-stationary period, only tentative conclusions can be drawn, especially as the typical RTT group engaged in low level vocalizations throughout the period from 5 to 24 months. What is noticeable though is that gestures were absent, initially in both groups and throughout the entire observation period in the typical RTT group, perhaps serving as an early indication of the difficulties in purposeful hand use which later typify RTT [3]. It is also clear that eye contact was the preferred mode of response, over gesture and vocalization, in both groups, a feature well documented in all variants of RTT [9].

The debate about similarities and differences between RTT and autism continues with some authors identifying the putative similarities in genomic imprinting which underlie ASD and other syndromes including RTT [46], as well as the similarities of the (transient) autistic-like features that can be observed during the regression phase of RTT [11, 48] or the persisting features of autism that can be observed, especially in milder forms such as PSV [19, 49, 50]. Other authors highlight the differences, for example in hand stereotypies, that can be observed when comparing the behaviors of individuals with RTT and ASD [45] and the greater social awareness exhibited by individuals with RTT [51, 52] which serves to distinguish them from those with ASD. In a previous study [27], we reported on the early presence of socio-communicative dysfunction in PSV, which may indeed be indicative of autistic features. We further suggested that these dysfunctions may persist beyond regression, but with age-specific profiles.

There are a number of interesting areas for future research related to the exploration of social reciprocity and the relationship between RTT and ASD. For example, it would be interesting to compare the profiles from the current study with profiles from studies into

early social reciprocity in children later diagnosed with ASD. It is not possible to take the results from this study alone and draw any direct inferences in relation to either ASD or typically developing children as only children with RTT were studied. Further studies involving both a typically developing control group and a cohort of children with ASD are necessary for this. Additional profiling of the children with RTT according to both variant and mutation type would also add valuable information to the existing knowledge about genotype-phenotype relationships in RTT [13-17]. It may then be possible to delineate similarities and differences in social awareness between children with RTT, its variants, ASD and typical development.

The lack of a control group, or a comparator group such as a cohort with ASD, could be seen as a limitation of the study. This lack of a comparison group means, for example, that no baseline for the observed/expected distinction was established. So too can the general problems which beset retrospective video analysis [37, 47, 53], for example, the contextual differences and lack of consistency between settings and situations, and the relatively short duration and gaps in availability of recordings for some participants. When taken together, these considerations do mean the findings must be interpreted with some caution.

However, in a field in which knowledge is limited, the study has served its stated aim of shedding further light on behaviors during the pre-regression phase of RTT and does respond to the need we previously identified to build a larger body of evidence to delineate different profiles for typical and atypical RTT [31]. It does seem possible to identify profiles of early social reciprocity (according to response to name), which may distinguish between typical RTT and PSV. When combined with the results of our previous studies, which examine other aspects of early socio-communicative, speech-language, movement and behavioral development [22, 24-27, 30, 31, 54, 55], early developmental profiles of children with typical RTT and PSV may be delineated more comprehensively. Its contribution towards the building of composite profiles for the differing variants of RTT is the value of the current study.

Acknowledgements

We would like to thank AM Kerr, G Pini, and M Zappella for their contribution to this study. This study was supported by the FWF P25241 (KDB), the Lanyar Foundation (337, 374), and BioTechMed – Graz. SB was supported by the Swedish Research Council (grant nr. 523-2009-7054).

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Chapter 7

Oculomotor Function in Individuals with Rett Syndrome

Published as:

Townend, G.S., van de Berg, R., de Breet, L.H.M., Hiemstra, M., Wagter, L., Smeets, E., Widdershover, J., Kingma, H., & Curfs, L.M.G. (2018). Oculomotor Function in Individuals With Rett Syndrome. *Pediatric Neurology*, 88, 48-58.
doi:10.1016/j.pediatrneurol.2018.08.022

Abstract

Background: Individuals with Rett syndrome (RTT) are notoriously reliant on the use of eye gaze as a primary means of communication. Underlying an ability to communicate successfully via eye gaze is a complex matrix of requirements, with an intact oculomotor system being just one element. To date, the underlying neural and motor pathways associated with eye gaze are relatively under-researched in RTT.

Purpose: This study was undertaken to plug the gap in knowledge and to further understanding of RTT in one specific area of development and function, namely oculomotor function.

Material and Methods: The eye movements of 18 girls and young women with RTT were assessed by electronystagmography (ENG). This tested their horizontal saccadic and smooth pursuit eye movements as well as optokinetic nystagmus and vestibulo-ocular reflex. Their results were compared to normative data collected from 16 typically-developing children and teenagers.

Results: Overall, the individuals with RTT demonstrated a range of eye movements on a par with their typically-developing peers. However, there were a number of difficulties in executing the ENG testing with the RTT cohort which made quantitative analysis tricky, such as reduced motivation and attention to test materials and low quality electrode signals.

Conclusions: This study suggests that individuals with RTT have an intact oculomotor system. However, modifications should be made to the ENG assessment procedure to combat problems in testing and add strength to the results. Further investigation into these testing difficulties is warranted in order to inform such modifications.

Keywords

Rett syndrome; Oculomotor function; Electronystagmography; Eye movements; Eye tracking.

Introduction

Individuals with Rett syndrome (RTT, OMIM 312750) are notoriously reliant on the use of eye gaze as a primary means of communication. Underlying an ability to communicate successfully via eye gaze is a complex matrix of requirements, with an intact oculomotor system being just one element. To date, however, the underlying motor pathways associated with eye gaze are relatively under-researched in RTT. The study reported in this paper was undertaken in order to plug this gap in knowledge and to further our understanding of RTT in this specific area of development and functioning.

Rett syndrome is a complex neurological disorder usually resulting from a *de novo* mutation in the gene encoding Methyl-CpG-binding protein 2 (*MECP2*), a transcriptional regulator [1-3] primarily, although not exclusively [4] expressed in neurons. The syndrome predominantly affects females and is typified by seemingly near normal development in the first six to 18 months of life followed by a deceleration in head growth and stagnation and regression in acquired skills, particularly loss of spoken language and purposeful hand use [5-7], accompanied by stereotypic hand movements and gait abnormalities [8-10]. Many studies have been conducted, utilizing animal models as well as humans and human cell lines, in an attempt to better understand and explain the biology of RTT [11-23]. Neuroimaging of the brain has revealed an overall reduction in cerebral volume and decreased dendritic arborization, in line with the noted microcephaly, with diffuse reductions in white matter and more focal reductions in gray, for example, the frontal lobe and cortex and the anterior temporal and dorsal parietal regions [22-24]. In contrast, however, the occipital cortex [23] and the tracts associated with visual function, specifically those within the posterior corona radiata [21] are relatively preserved.

Some studies have focused on the expression and distribution of *MECP2* in the brain and found it to be reduced in certain areas, with the brainstem and thalamus exhibiting the greatest reductions in *MECP2* protein expression [25]. These findings accord with the fact that many of the secondary features associated with RTT, such as cardiorespiratory and sleep disturbances, problems with cardiovascular and sensory regulation, and apraxia/dyspraxia, arise from disruptions in brainstem functioning. Features such as epilepsy, dystonia and other movement disorders, and orthopedic problems are more related to disturbances at a cortical or extrapyramidal level [26] and can be at least partly explained by the structural studies reported above which have found reductions in white and grey matter, with reduced synaptic development and neuronal connectivity.

Alongside these areas of deficit, however, one of the most frequently reported observations is the use of “intense eye communication – ‘eye pointing’” [8, p.946, 26] by individuals with RTT who otherwise struggle to communicate through more conventional means. The complex interaction of dyspraxia, dystonia, ataxia and other motor features affects the speed, reliability, control and coordination of movements. Yet, individuals with RTT are usually thought to demonstrate good functional use of ‘eye pointing’ or eye gaze

for communication [6, 27], which opens the question of whether the neural and motor movements associated with eye gaze are (relatively) less affected than other pathways. This has been evidenced to some extent by studies described above [23, 21], in addition to which there have been a number of studies examining visual evoked potentials and aspects of visual acuity in individuals with RTT as a measure of brain function [28-34]. Such studies have investigated the afferent or peripheral visual pathways which convey visual signals from the retina to the brain, and have found these pathways to be intact, although there are indications of disruption to visual processing at a higher, cortical level, which may deteriorate with age. At another level of analysis, Jain et al. [35] examined, postmortem, the eyes of two individuals with RTT and reported no gross or microscopic changes when compared with controls. They also tentatively explored the role of *MECP2* in vision, by comparing the levels of *MECP2* to be found in the retinas of the individuals with RTT versus the controls and concluded that “the normally limited expression of *MECP2* in visual pathway neurons may underlie the intact vision observed in RTT” [p.35]. However, studies focusing on the efferent visual pathways in RTT, involving the oculomotor system, are much rarer. Koslowe et al. [29] did consider visual tracking as one parameter and concluded that although the optic nerve appeared to be normal in RTT, the individuals in their study demonstrated significant deficits in their visual tracking skills. It is this gap in knowledge – of the efferent visual system of individuals with RTT – that the current study seeks to plug.

Eye Movements and the Oculomotor System

Five different types of eye movements – both voluntary and reflex – have been identified [36, 37]. Four of these can be described as visual-ocular responses (provoked by images moving across the visual field) [38]. These are: saccades, smooth pursuit (SP), optokinetic nystagmus (OKN), and vergence. The fifth, or vestibulo-ocular reflex (VOR), is in response to movement of the head which is detected by the vestibular system [39-41]. These five movements share the common aim of stabilizing images on the retina (specifically on the fovea, the part of the retina with the sharpest visual acuity), either by holding gaze and image steady or by shifting gaze to bring images to the fovea independent of any head movement. In essence, saccades could be said to be gaze shifting whilst SP, OKN, vergence and VOR are gaze holding mechanisms [38, 42]. In addition, some researchers [37, 42-46] describe the process of fixation – the act of holding an image on the fovea to allow time for visual analysis of the image. The study we report in this paper, conducted with individuals with RTT, focuses on examination of saccades, SP, OKN and VOR.

Eye Tracking and Rett Syndrome

In recent years, eye tracking technology has been increasingly used by individuals with RTT as a way of accessing communication and developing a means of self-expression. Eye tracking technology has also been used as a medium for assessing the cognitive and

receptive language skills of individuals with RTT [47-57].

Most common eye tracking systems used for communication depend upon a camera measuring the reflection of near infra-red light on the cornea and pupil of each eye to determine where the gaze is directed on screen [58]. Grids or 'pages' of pictures and/or words are presented and selected by the user fixing his or her gaze on an item of choice for a specified length of time ('dwell time'). In this, saccades, SP and fixation come into play, as does the VOR if the head moves or tilts. Visual attention is also a factor in how an individual directs his or her gaze.

There is a presumption that eye tracking technology is pertinent for individuals with RTT because of their ability to communicate with their eyes in the context of loss of purposeful hand movement [59-61]. Yet little research has been conducted into the functioning of the oculomotor system in RTT. For example, to consider whether this system is affected by apraxia and delayed reaction time in the same way that other body movements are affected. Research has been conducted into oculomotor apraxia in other client groups [62] and into the relationships between other clinical disorders and eye movements [63, 64] but these findings cannot necessarily be extrapolated to RTT, neither can results from neurotypically-developing individuals be presumed to apply. Research into the mechanisms underlying successful use of eye gaze in individuals with RTT is warranted to better our understanding of this complex rare disease.

Electronystagmography

Examination of eye movements may be performed through direct observation, for example, by the examiner moving a finger or penlight in front of the participant's gaze to test saccades or SP, or spinning the participant in a chair before bringing them to a sudden halt to test VOR. The tests can also be conducted more objectively through electronystagmography (ENG) [65]. This involves the placement of electrodes around the eyes (usually above, below and to the sides, with a ground electrode on the forehead) so that electrical activity in the eyes can be detected, fed into a computer where the signal is amplified and recorded, and charts can be produced – if desired – which graphically illustrate the various oculomotor movements. Electrical activity is registered by detecting the corneo-retinal potential. In this, the retina acts as the negative pole and the cornea as the positive.

The Department of Otorhinolaryngology (ENT) at Maastricht University Medical Center (MUMC+) – an international center specializing in central and peripheral vestibular disorders and disorders of the oculomotor system – regularly conducts oculomotor assessments through ENG. By applying these tests to the individuals with RTT who were coming into the hospital, therefore, we aimed to discover more about the impact (if any) that disturbances in *MECP2* may exert on the oculomotor system of individuals with RTT.

Materials and Methods

The study was conducted as a collaborative venture between the Rett Expertise Centre Netherlands – GKC and the ENT Department at MUMC+. It was performed in accordance with institutional guidelines and the 1964 Declaration of Helsinki. Ethical approval for conducting oculomotor research with individuals with Rett syndrome was granted by the MUMC+ Medical Ethics Research Committee (NL57673.068.16/METC162027) and written informed consent was obtained from the participants/parents for use of their anonymized data.

Tests of SP eye movement, saccades and OKN were performed. In addition, the VOR was tested.

Participants

The RTT cohort were recruited from individuals with Rett syndrome admitted to MUMC+'s Pediatric Intensive Care Unit (PICU) for three-day evaluation of brainstem functioning; the oculomotor assessments took place in the ENT department during their hospital stay.

The control group were recruited from families of hospital employees as part of a larger, separate hospital study collecting normative ENG data for children and teenagers.

Test Conditions, Preparation and Procedure

The early assessments were performed using the BalanceLab Vestibular Research Laboratory, Version 2.3.0, build 969; during the course of the study this system was upgraded to KingsLab, Version 1.6.1, build 740 (© Maastricht University 2015). Standard procedure involved placing nine disposable Ambu Blue Sensor electrodes (children NF-50-K/W/12, adults N-50-K/25) above, below and to the sides of each eye (temporal, nasal, supra- and infraorbital) with a ground electrode on the forehead. During the study this was modified to three electrodes, two placed temporally (at the lateral canthus of each eye) and one on the forehead. In order to ensure good adherence and impedance, the skin around each participant's eyes, nose and cheeks was cleansed with a fat solvent petroleum ether and gently scoured with a skin rasp prior to electrode fixation. These preparations were performed in an outer room before proceeding into the test room proper. Testing with electrodes was selected as the preferred medium for the study rather than, for example, using video goggles, as professional experience indicated that electrodes would give a signal even if the participant's eyes were not fully open and fewer instructions would be required to complete the assessments.

All tests were conducted by a well-trained examiner in a semi-darkened room with the only illumination being the beamer which projected the images onto the wall during the three oculomotor tests. The beamer was turned off for the final test, the rotatory chair (torsion swing) test, so that the room was then in total darkness. Participants were seated

on a fixed chair in the center of the room, at a distance of 165-170 cm from the wall onto which the images were projected. Once seated they were secured by a safety belt and the electrodes were plugged into a small transducer worn around the participant's neck which acted as an interface to connect to the computer. Any participants who were unable to sit independently were seated on their parent's lap and, to minimize any head movements, the parent was asked to hold their child's head.

The examiner remained in the outer room from where he/she operated the computer system controlling the tests; an infrared video camera and two-way speaker system allowed for constant monitoring and communication between the examiner and participants. Minimal verbal instruction was given, with the participants told simply to look at the pictures that would appear on the wall. At all times, at least one parent and a medical professional were present in the test room to provide reassurance and give additional instruction or encouragement if necessary. For example, parents might give a simple commentary on the images as they appeared ("oh, there's dad", "I can see a white horse, a bird, a dog").

Test Components and Data Analysis

Where possible, signals from both eyes were recorded and combined after amplification. The four ENG tests were conducted in sequence in a single session, with calibrations measured at the start and in between the tests. Where only three electrodes were used, the signals were recorded on one channel only, either using the right side channel (OD) or the left (OS). In the first instance, the RTT cohort and control group values were plotted against commonly-used adult reference norms and then compared with each other as the control group values were being used to set a new normative reference for a younger population.

Calibrations were performed by asking each participant to follow a single image moving in a saccadic pattern with 10° intervals from the center to the left and to the right in a horizontal plane (a total movement of 20°). Where calibration proved difficult on the first attempt, it was repeated, sometimes several times. Calibrations were deemed to be of a good or high quality if the signals gave clear recordings for both eyes in both vertical and horizontal planes, and were in the expected direction and time frame with minimal drift (less than 5°/second). They were said to be of poor or low quality if there was a nil response, a signal was recorded for only one eye or in one direction, or there was too much drift (greater than 5°/second) due to the signal to noise ratio (i.e. signal fluctuation in the absence of eye movements). Continuing poor calibrations did not automatically lead to abandonment of testing. If the quality of signals was too poor or unreliable to yield quantitative results that could be analyzed automatically by the computer, qualitative judgements were made from observation and visual inspection of the data by the examiners. Each type of eye movement was judged to be present or absent where there

was a clear and readable signal or marked as 'unsure' if (1) a good calibration had not been achieved previously and/or (2) the trace on a particular test could not be read due to a nil response or too much drift despite a previously good calibration. All judgements were reached through consensus, with at least two, usually three, examiners working together.

Smooth pursuit eye movements were tested by asking each participant to follow a single image moving horizontally to the right at a frequency of 0.2 Hz and a constant speed of $11.3^\circ/\text{second}$ until it reached 10° eccentricity, at which point it abruptly changed direction and began moving to the left. The parameters of interest were: (1) presence of SP eye movements, (2) if present, whether SP was completely smooth, and (3) the percentage 'gain'. A valid SP movement was defined as an eye movement with its direction and phase corresponding to the stimulus, with a gain falling between 85% and 105% (the adult reference value). SP was judged to be completely smooth if there were no catch up saccades or drift noted.

Horizontal saccades were tested by asking each participant to look at a single image moving abruptly at random intervals, 10° to the left and right of center. The parameters of interest were: (1) presence of saccadic eye movements to both sides, (2) dysmetria (eyes not moving far enough to place the image on the fovea at first attempt so needing to make a minor correction saccade), (3) latency (time delay between stimulus and response), and (4) maximum velocity (maximum speed of movement, comparing between both eyes and between stimuli to the right and left, where possible). In addition, the examiner made a judgement about whether the eye movements were conjugate. A valid saccade was defined as eye movement in the same direction as the moving image, occurring in under 249ms and with a maximum velocity below $235^\circ/\text{second}$ to both the right and the left (the adult reference values).

Optokinetic nystagmus was tested by asking each participant to look at a pattern of images that filled the wall and moved alternately to the right and to the left, at speeds that increased from 5 to $48^\circ/\text{second}$ at 4.72° intervals. The parameters of interest were: (1) presence of OKN, (2) whether OKN was 'correct' (fell within the expected gain range), and (3) mean maximum slow component velocity (SCV) (also known as slow phase velocity). A valid OKN was defined as a nystagmus moving in the opposite direction to the moving images, with a mean maximum SCV to both the right and the left of below $23^\circ/\text{second}$ (the adult reference value).

Vestibulo-ocular reflex was conducted through a sequence of bi-directional halfway rotations of the chair on which the participant was seated, while in complete darkness. This is also known as the *torsion swing test* and stimulates the vestibular system in order to evoke a horizontal nystagmus. The tests were performed using sinusoidal rotation with a frequency of 0.1 Hz and a peak velocity of $100^\circ/\text{second}$ during one minute. The parameters of interest were: (1) presence of VOR, and (2) percentage 'gain'. A valid VOR was defined as a series of consecutive nystagmuses in the same direction as the movement of the chair and the head, within a gain range of 30 to 65% (the adult reference value).

During the calibrations, and tests of SP and saccades, single images of faces were projected onto the wall. For the RTT cohort, the faces were those of the participant's parents or other close family members, supplied as a digital image by the family prior to the test; for the control group, familiar cartoon characters were used (e.g. Bert and Ernie from Sesame Street). For the OKN test, cartoon images of animals were used across both groups.

Statistical Evaluation

Descriptive analyses of data were performed using IBM SPSS version 24. More rigorous statistical analyses were not undertaken in order to avoid bias as there were large gaps in quantitative data for the RTT cohort. Further details – and potential explanations – for this will be given below.

Results

The RTT cohort consisted of 18 girls and young women aged between two years seven months and 25 years 11 months (mean age nine years seven months, SD 6:5), all of whom had a clinical and genetic diagnosis of Rett syndrome.

The control group consisted of 16 children aged between three years six months and 18 years seven months (mean age seven years eight months, SD 4:0), nine males and seven females, all of whom had a normal clinical evaluation (Table 1).

Table 1. Participant overview.

Group	Mean age (years : months)	Range (years : months)	SD
RTT n=18	9:7	2:7 – 25:11	6:5
Control n=16	7:8	3:6 – 18:7	4:0

ENG Findings

Five children in the control group were assessed using nine electrodes. Their results are based on their ODS (combined right and left channel) scores. Eleven in the control group were tested with only three electrodes. Of these, 10 of 11 were recorded on the right side channel (OD) and one of 11 on the left (OS).

Seventeen of the RTT cohort were assessed using nine electrodes. For three of 17, the signals could not be read for the right eye so the results are based on the recording of their left eye only; for the remaining 14 of 17, the analysis is based on the combined ODS score where possible. One child from the RTT cohort was tested with three electrodes only, with her results recorded on the OD channel.

Calibration

All of the control group achieved a good calibration at the start of the session; these were repeated again before the torsion swing tests.

Calibration proved more difficult with the RTT cohort. For only four of 18 was the calibration deemed to be good or of high quality; for two of 18 horizontal calibration was better than vertical and for three of 18 calibration was only possible on one eye. For the remaining nine of 18, the calibrations were regarded as poor or of low quality, giving unreadable signals. In one or two cases a better calibration was achieved with repetition.

An overview of the main ENG findings – especially the presence or absence of the four assessed movements (SP, Saccades, OKN and VOR) – is given in Table 2, while more detailed aspects pertaining to these movements are presented in Table 3.

The ENG results were also grouped according to each type of assessed eye movement, details of which are presented below.

Smooth Pursuit

As shown in Table 2 and Fig. 1, SP was present in all of the control population. However, it could not be reliably determined in a third of the RTT cohort. In all unclear cases, a coding of ‘unsure’ was given rather than ‘no’ (not present) because none of these cases achieved a good calibration prior to the test of SP. One of the six achieved a better calibration following the SP test, before the test of saccades. Potential reasons for the poor calibrations and variability within samples will be explored in the Discussion section.

Judgements of whether SP was completely smooth could only be made in cases where SP was detected as present, that is, a decision could be made for all 16 of the control subjects but for only 12 of the RTT cohort. A portion of both the control and RTT groups was found not to have smooth movements even though SP was present (Fig. 2). In some cases, one or two ‘good’ SP traces could be found within a longer sample which, if taken overall, would not have been deemed ‘good’. This required a well-trained examiner to analyze, and where possible, clean up the signals to remove extraneous ‘noise’. In Fig. 3 several focused SP eye movements are demonstrated in the middle of the recording although these are not smooth.

Likewise, a calculation of percentage gain could only be made if SP was judged to be present and, even then, the signal was not always good enough to give clear or reliable quantitative data. Gain could be calculated for all of the controls but for only two thirds of the RTT cohort for whom SP was deemed to be present (Table 3 and Fig. 4).

Table 2. Overview of main ENG findings.

Group	Smooth Pursuit		Saccades		OKN		VOR	
	Present % (n/N)	Completely smooth	Present	Dysmetria	Present	Correct	Present	
RTT n=18	Yes	67% (12/18)	58% (7/12)	72% (13/18)	-	83% (15/18)	60% (9/15)	86% (12/14) ¹
	No		17% (2/12)	-	85% (11/13)	-	-	-
	Unsure	33% (6/18)	25% (3/12)	28% (5/18)	15% (2/13)	17% (3/18)	40% (6/15)	14% (2/14) ¹
Control n=16	Yes	100% (16/16)	75% (12/16)	100% (15/15) ²		100% (16/16)	100% (16/16)	100% (16/16)
	No	-	25% (4/16)	-	100% (15/15) ²	-	-	-
	Unsure	-	-	-	-	-	-	-

¹Only 14 of 18 of the RTT cohort were tested for VOR on torsion swing. ²Only 15 of 16 of the control group were tested for saccades

Table 3. Scores on individual ENG parameters.

Group	Smooth Pursuit		Saccades		OKN		VOR	
	Gain ³ (85-105%)	Latency ³ (<249ms)	Max velocity to R ³ (>235°/sec)	Max velocity to L ³ (>235°/sec)	Mean max SCV to R ³ (>23°/sec)	Mean max SCV to L ³ (>23°/sec)	Gain ³ (30-65%)	
RTT n=18¹	N	8	9	8	10	10	7	
	Min - Max	83 - 104	160 - 356	352 - 884	299 - 1433	13 - 53	10 - 48	42 - 90
	Mean	96	203	509	552	32	32	65
	SD	8.04	59.13	185.28	369.59	11.63	10.99	19.34
Control n=16²	N	16	15	15	16	16	16	
	Min - Max	79 - 111	104 - 140	321 - 640	315 - 578	24 - 51	29 - 45	26 - 119
	Mean	94	120	466	459	41	39	71
	SD	9.59	11.72	87.36	91.92	7.81	4.65	22.84

¹As quantifiable results could not be obtained for all of the RTT cohort, the results in this table are not always based on N=18 but vary for each test.

²Only 15 of 16 children in the control group were tested for saccades; one child was not. ³The commonly used adult reference values are given for comparison.

Figure 1. Smooth pursuit present
This shows % of total N for each group.
 RTT n=18, Control n=16

Figure 2. Smooth pursuit completely smooth
n = Participants in each group for whom SP is present. RTT n=12, Control n=16

Figure 3. Trace recording of smooth pursuit eye movement

Figure 4. Smooth pursuit percentage gain
n = Participants in each group for whom gain could be measured. RTT n=8, Control n=16
The two solid black lines indicate the minimum and maximum adult reference values (85 to 105%).

Saccades

All of the control subjects who were tested for saccades demonstrated reliable saccades with no dysmetria. One participant was not tested due to fatigue and reduced cooperation. All of the RTT cohort were tested but neither judgement could be reliably determined for a portion of this group (Table 2; Fig. 5 and 6). Latency and velocity could only be calculated where saccades were deemed to be present. Although the signals were not clear enough in all cases to yield quantitative results, it did appear from visual inspection that the RTT cohort tended towards a longer latency than the control group (Table 3; Fig. 7 and 8).

Conjugation

This was difficult to assess in cases where only one eye was measured, but from observation by a trained examiner, and/or where two eyes were measured, all participants (RTT and controls) were judged to demonstrate conjugate eye movements.

Figure 5. Saccades present (to R & L)
 This shows % of total N for each group.
 RTT n=18, Control n=15

Figure 6. Dysmetria present
 n = Participants in each group for whom
 saccades are present. RTT n=13, Control n=15

Figure 7. Latency of saccades
 n = Participants in each group for whom latency
 could be measured. RTT n=9, Control n=15.
 The solid black line indicates the adult reference
 value (<249ms).

Figure 8. Maximum velocity of saccades to R and to L
 n = Participants in each group for whom maximum
 velocity could be measured. RTT n=8, Control n=15
 The solid black line indicates the adult reference
 value (>235°/second).

Optokinetic Nystagmus

All of the control group demonstrated OKN, which in all cases was also judged to be correct in that it fell within the expected gain range. As with the previous oculomotor tests, it was not possible to determine whether a portion of the RTT cohort had OKN. This type of eye movement could, however, be provoked in a higher number of cases than for SP or saccades, even if the signal response did not yield clear quantitative data for analysis (Table 2; Figs. 9 to 11). In two of the RTT cohort, the OKN was only elicited at lower velocities but nonetheless judged to be present, in three other RTT participants the OKN gain was relatively low and classified as 'correct' though borderline, and one further participant demonstrated a small asymmetry, with a lower frequency OKN and a negative exponential slow phase.

Figure 9. OKN present

This shows % of total N for each group.

RTT n=18, Control n=16

Figure 10. OKN correct

n = Participants in each group for whom OKN

is present. RTT n=15, Control n=16

Figure 11. Mean maximum SCV

n = Participants in each group for whom mean maximum SCV could be measured.

RTT n=9, Control n=15.

The solid black line indicates the adult reference value (>23°/second).

Figure 12. VOR present

This shows % of total N tested on torsion swing for each group.

RTT n=14, Control n=16

Figure 13. VOR gain

N = Participants in each group for whom VOR could be measured.

RTT n=7, Control n=16

The two solid black lines indicate the minimum and maximum adult reference values (30-65%).

Vestibulo-Ocular Reflex

All of the control group demonstrated the presence of VOR with a measurable gain. Four of the RTT cohort were not tested as their parents declined the torsion swing. However, this test did produce the highest set of positive responses in the RTT cohort with VOR detected in 85% of those tested, even though the gain could only be quantified in half of these cases (Tables 2 and 3; Fig. 12 and 13). In five of the RTT participants, the fast phase velocity was noted, incidentally, to be relatively slow.

Discussion

This study investigated the oculomotor function of girls and young women with Rett syndrome. The results of their assessments were compared with those of a similarly-aged neurotypical control group, against a background of the commonly used adult normative values.

Overall, where their responses could be observed and/or measured, the individuals with RTT demonstrated a range of eye movements on a par with their neurotypical peers. For example, all of the control group and the majority of girls with RTT who gave a measurable result showed that they possessed SP and saccadic eye movements, OKN and VOR. When the scatter plots were inspected visually, no major differences between the two groups were immediately apparent across most of the quantifiable measures (SP gain, saccades velocity, OKN mean maximum SCV, and VOR gain), except for occasional outliers, when compared with the adult reference norms. Likewise, both groups included individuals for whom SP was not smooth. This phenomenon was not restricted to the RTT population, and is something often considered to be an artefact of variable attention, especially when testing children. Two areas of potential difference are (1) saccades latency, where the RTT cohort seemed to exhibit a longer latency, and (2) VOR, where it was noted incidentally that the RTT group demonstrated a somewhat slower fast phase velocity. As the power was so low, however, this difference could not be tested for significance, and the VOR test itself was brought into question by the unusually broad range of VOR gain recorded across both groups, which pointed towards possible errors in recording or calibration for this specific test. Longer saccades latency could be of relevance, however, and should be investigated further in the future.

The real difference between the two groups, though, lay in the high number of RTT individuals whose responses could not be quantified or classified as present or absent with any certainty. In this respect the difficulties in executing the ENG testing with the RTT cohort were highlighted and the resulting low powers and risk of bias meant that no statistical analyses were performed. Poor signal to noise ratios, with a lot of drift, interfered with the quality of the recordings such that the signals were not clean and were difficult to read. In many cases taking a whole signal yielded poor average values but, with an experienced tester, it was often possible to isolate one or two good responses from a longer

trace. Wherever a couple of good responses could be observed then that was taken as an indication of whichever target movement was in question. Many of the RTT cohort struggled to achieve a good calibration, only managing this in one eye in some cases or after repeated attempts. If a calibration was achieved, however, this was an indication that saccadic eye movement was possible even if they were unable to perform consistently well on the test of saccades itself. In all cases where saccades were recorded these were present to the right and to the left in both the RTT and control groups.

At face value the problems in achieving a good calibration and in testing in general seemed to relate to multiple factors, including blinking and/or extraneous head movements, participants touching or pulling at the electrodes which loosened them and led to poor connectivity, and reduced motivation, interest in and attention to the test materials. Indeed, the variability in performance exhibited by some individuals would typically be seen as indicative of an attentional issue in neurotypical children. Attention plays an important role in OKN especially, and, if VOR is shown to be intact following a nil or unclear OKN response, this can confirm that attention was likely the issue as VOR is evoked without a visual stimulus. One further factor to be considered, though, is that the need for speed in preparation of the skin and attachment of the electrodes, to reduce the possibility of irritation and discomfort, may have led to reduced adherence of the electrodes and hence conduction of the signals was impeded. During the study period, there was an attempt to address this issue by reducing the number of electrodes from nine to three. In this way, recording was necessarily reduced to one channel only (either OS or OD). Whether this is an effective remedy, or whether alternative forms of testing which do not require electrodes will yield more complete and reliable results, remains to be seen with continued testing of a larger cohort.

The need for an intact oculomotor system is but one element of the jigsaw when considering the use of eye pointing or eye gaze for communication. Sargent et al. [66] offer a useful working definition of eye pointing, suggesting that it is the “context-relevant, controlled and intentional use of gaze in order to direct one or more partner’s visual attention to any item or object for a deliberate communicative purpose” (p.479). They further conclude that “eye-pointing can be seen as the integrated outcome of a combination of visual, social, cognitive and motor skills” (p. 482), and that careful evaluation of this matrix of skills is required if we are to reach a common understanding of all that is involved in successful use of eye pointing, or eye gaze, for communication. The starting point is that of assessing whether an individual can maintain and shift fixation of static and moving targets. It is at exactly this level of basic oculomotor skill that our study was aimed.

Where any individual with RTT appears to be ‘failing’ or struggling to use eye gaze, or eye tracking technology, for communication, an assessment of their oculomotor system is a starting point for unravelling where the point of breakdown may lie. To ensure a valid and helpful result, however, traditional ENG testing procedures need to be adapted and new

methods of assessment should be developed. Reasons for the difficulties encountered in the ENG assessments undertaken in this study and possible options for change will be explored in phase two of the study [67].

Conclusion

The data obtained from this study indicate that individuals with RTT have largely intact oculomotor functioning but their responses on traditional ENG assessment are hindered by issues such as poor attention.

Declarations of Interest

None

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Chapter 8

Challenges in Evaluating Oculomotor Function in Individuals with Rett Syndrome Using Electronystagmography

Published as:

de Breet, L.H.M.[#], Townend, G.S.[#], Curfs, L.M.G., Kingma, H., Smeets, E., Lucieer, F., Widdershoven, J, & van de Berg, R. (2019). Challenges in evaluating oculomotor function in individuals with Rett syndrome using electronystagmography. *European Journal of Paediatric Neurology*. 23(2), 262-269. doi:10.1016/j.ejpn.2018.12.003
([#]shared first authorship)

Abstract

Background: Rett syndrome (RTT) is a neurological disorder characterized by a broad spectrum of symptoms. Communication is a major area of difficulty. Use of eye tracking technology offers a potentially effective method of communication when underpinned by intact oculomotor function. In this study, oculomotor function was assessed using electronystagmography (ENG). However, challenges were encountered when examining individuals with RTT.

Purpose: To improve oculomotor examination in individuals with RTT by evaluating the challenges encountered during ENG examination.

Material and Methods: Oculomotor function was examined in 17 girls and young women with RTT and 16 typically developing (TD) individuals using ENG. Observational analysis of both performance and results indicated that challenges in examination were mainly related to quality of attention and quality of signals. Subsequently these outcome values were explored quantitatively according to percentage looking time for attention and drift for signal quality.

Results: A significantly reduced level of attention and suboptimal electrode signals were evident in the RTT group when compared with the TD group for all tests except torsion swing.

Conclusion: The challenges in testing confirm that regular oculomotor examination should be adjusted to meet the needs of individuals with RTT. It is hypothesized that the RTT group's higher quality of attention on the torsion swing can be explained by the more forceful vestibular rather than visual-ocular stimulus operating in this test. Suggested adaptations include reducing the number of electrodes, changing the picture stimuli and bringing them closer, performing observational assessments rather than ENG, and using virtual reality goggles.

Keywords

Rett syndrome; Oculomotor function; Electronystagmography; Attention; Electrode signals.

Introduction

Rett Syndrome (RTT) is a rare neurological disorder almost exclusively affecting females. The syndrome is characterized by a broad clinical spectrum of signs and symptoms with an overall pattern of stagnation, regression and possible partial recovery [1-3]. Initially, children show a period of 6-18 months of seemingly normal development. Thereafter, an arrest occurs in their development followed by a progressive loss of acquired skills such as purposeful hand function and spoken language [4]. Further comorbidities include autonomic dysfunction, breathing irregularities, scoliosis, gastro-intestinal problems, reduced somatic growth, osteopenia, gait apraxia, and frequent seizures which may or may not be epileptic in origin [4, 5].

The investigation described in this paper is the second stage of a two-part study based upon the premise that girls with RTT communicate through eye movements [6-8]. Typically, individuals with RTT demonstrate a loss in ability to communicate through traditional means (e.g. speech, signing) but retain the ability to communicate through eye gaze or eye-pointing behavior. The use of eye tracking technologies to facilitate communication is increasingly promoted with this population [9-11]. In the first part of the study [12], electronystagmography (ENG) was used to test the eye movements of girls with RTT. Saccades, smooth pursuit (SP) and optokinetic nystagmus (OKN) [13-15] were examined as indicators of oculomotor function while torsion swing (or the vestibular-ocular reflex (VOR)) was assessed as a measure of vestibular function because eye movements are closely related to the function of the vestibular organ. For all of these tests, attention is a particularly crucial element.

In recent years, a number of studies have explored aspects of attention in girls with RTT. Fabio et al. [16, 17], for example, have considered selective attention and evaluated the ability of individuals with RTT to look to a target object in preference to other non-target objects or faces (of assessor or caregiver). They also looked for evidence of joint attention behaviors, such as looking between target object and caregiver. Whilst identifying impairments in selective attention to target objects and a heightened interest in social stimuli, they also found that selective attention to objects could be improved through containment of hand stereotypies and through training. This, Fabio and colleagues concluded, had important implications for communication and cognitive functioning, as increases in distractibility and in responses to irrelevant stimuli interfered with processing of relevant information. Rose et al. [18-20] have also explored the selective attention of girls with RTT, as well as their ability to maintain attention. Their most recent study [20] lends support to the fact that individuals with RTT demonstrate impairments in selective attention, while their earlier studies [18, 19] also show that they are capable of maintaining attention on a stimulus and can orient relatively quickly to the appearance of a target in the visual field. However, individuals with RTT demonstrate more difficulty with sustained attention when compared to a healthy control group [18, 21], and have been found to be

slower to engage with moving objects, to be more distractible, and slower to re-engage [18]. Thus, attention can be divided into categories such as ‘selective’, ‘shifting’, ‘sustained’ and ‘joint’ attention, with selective being the ability to focus on the relevant or target stimuli, shifting being able to disengage at one location and re-engage attention at a new location, sustained attention being the ability to maintain focus over an extended period [19] and joint attention being able to share a point of common reference with another person. Shifting attention is of interest in the present study as it follows a saccadic pattern of eye movement. Shifts are reactive to external changes in the visual field when under exogenous control, for example, in response to a moving object [19].

At the end of the first part of the study, it was concluded that the oculomotor function of individuals with RTT appeared to operate within normal limits [12]. While performing the ENG examinations, however, challenges arose with the quantitative data analysis as fluctuating and/or noisy signals were often encountered. It was hypothesized that these might be the result of a lack of attention and/or suboptimal quality of electrode signals, respectively. It is important to acknowledge these problems, since they should not be interpreted erroneously as a pathological finding, but rather as an artefact. The chief goal of this second part of the study, therefore, is to evaluate the occurrence of these artefacts in females with RTT when compared to healthy, typically developing children, and to propose possible solutions for obtaining more reliable and reproducible oculomotor results when assessing individuals with RTT.

Material and Methods

The study was conducted as a collaborative venture between the Rett Expertise Centre Netherlands-GKC and the ENT Department at MUMC+. It was performed in accordance with institutional guidelines and the 1964 Declaration of Helsinki. Ethical approval for conducting oculomotor research with individuals with Rett syndrome was granted by the MUMC+ Medical Ethics Research Committee (NL57673.068.16/METC162027) and written informed consent was obtained from the participants/ parents for use of their anonymized data.

Participants

Two groups of participants were recruited: (i) an experimental group who all had a clinical and genetic diagnosis of RTT, and (ii) a similarly-aged typically developing (TD) control group. The RTT cohort was recruited from inpatients undergoing three-day evaluation of brainstem functioning at the Pediatric Intensive Care Unit (PICU) of MUMC+ whilst the controls were children of hospital employees, recruited as part of a separate study collecting normative ENG data for children and teenagers.

Procedure

Oculomotor and vestibular assessments were conducted using ENG, with data recorded in Kingslab Version 1.6.1 (© Maastricht University 2015). Participants were seated on a fixed chair in a semi-darkened room with electrodes placed around their eyes. For the RTT group, photographs of individual family members and images of animals were projected onto the wall in front of them. For the TD children, cartoon characters and images of animals were used. Each participant was required to follow the movements of the digital images with their eyes, without moving their head. If required, their head was held stationary by a parent. Minimal verbal instruction was given. Oculomotor movements were registered by the electrodes and transmitted to the computer via a transducer worn around the participant's neck.

The testing procedure began with calibration. The calibration routine was also repeated between tests if necessary, to obtain as reliable a calibration as possible for all four tests. Saccades, SP and OKN were tested and, finally, the torsion swing test was performed in complete darkness to assess VOR. Visual acuity was not assessed in this study. Further elaboration of these procedures can be found in the description of the first part of the study [12].

Analysis

Observational Analysis

Trained clinicians evaluated the quality of all measurements (calibration, saccades, SP, OKN and torsion swing test) using observational analysis. Of particular interest in this part of the study were the quality of the participants' attention and the quality of the signals. Outcome values were determined in consensus and quantitative analysis was then performed for each cohort.

Calibration and Saccades

A valid saccadic eye movement was defined as an eye movement in the same direction as the moving image within a timeframe of <249ms, maintaining fixation until the end of the saccadic stimulus.

Attention was measured as percentage looking time, according to the formula: (total valid saccadic eye movements made by participant / total saccadic stimuli) x 100%. One saccadic stimulus was defined as one movement of the stimulus from the left to the right, or vice versa. The quality of the signals was classified by the degrees of drift, which reflected the signal to noise ratio (SNR) [22-24]. "Drift" referred to the number of degrees by which the signal fluctuated over time, in the absence of eye movements [22, 24]. This was measured in degrees per second (°/s). Three groups were used to classify the quality: <2°/s, 2-5°/s and >5°/s.

Smooth Pursuit

A valid pursuit eye movement was defined as an eye movement with its direction and phase corresponding to the SP stimulus. Fixation had to remain until the end of one cycle of stimulation. Blinks were not considered to be a loss of fixation.

Attention was measured as percentage looking time, by: (total valid cycles of pursuit eye movements made by participant / total cycles of SP stimulation) x 100%. One cycle of pursuit was defined as a movement starting at one side, moving fluently to the other side and back again. Quality of signals was measured in the same way as calibration and saccades.

OKN

OKN was defined as the presence of a nystagmus, in the opposite direction from the moving images.

Attention was measured as percentage looking time, this time according to: (total number of seconds looking at moving images on the screen / total number of seconds of moving images on the screen) x 100%. The exact timing of the change in direction of the nystagmus and the change in direction of the moving images had to coincide. The stimulus velocity was gradually built up to 48°/s. For stimuli below 10°/s the response is normally poor, so these data were excluded from analysis. Eye movements of a significantly higher slow component velocity (scv) (°/s) than the velocity of the images on the screen, as judged by a trained clinician, were considered to be an eye blink or another artefact. The quality of the signals was evaluated as “quantifiable” or “unquantifiable”. The signal was quantifiable if drift was less than 5°/s, and unquantifiable if the drift was 5°/s or more.

Torsion Swing Test

The torsion swing (or VOR) was defined as a cycle of consecutive nystagmuses in the same direction as the movement of the chair and head.

Attention was measured as percentage looking time, by: (total correct nystagmic responses per stimulus / total of stimuli) x 100%. A correct nystagmic response was defined as a nystagmic response in phase with the torsion swing head movement. A minimum response of 50% per stimulus was considered a positive response. The quality of the signals was evaluated as “quantifiable” or “unquantifiable”. Once again, the signal was quantifiable if the drift was less than 5°/s and unquantifiable if drift was above this.

Duration of Each Test

The duration of each test was based on the performance of the individual. In cases where attention was judged to be good (reflected by a high percentage of looking time) and high quality of signals (reflected by a low degree of drift) only a couple of stimuli were required before continuing to the next test. In cases of absent or poor attention during trials, more stimuli were required in order to get as representable and reproducible results as possible. The minimum and maximum number of stimuli were respectively 5 and 72 for calibration,

10 and 60 for the saccadic test, for the pursuits 4 and 13 respectively, for the OKN 42 to 102 seconds and for the torsion swing 7 to 11 half-way turns.

Statistics

The primary outcomes were quality of attention (measured in percentage looking time) and quality of signals (measured in drift), during testing of the oculomotor function in individuals with RTT. Percentage looking time was classified into 5 groups, with the first set at 0% and incremental band widths of 25% for each subsequent group. Data were analyzed using IBM SPSS Statistics V.24 (IBM Corporation, New York, United States of America). The Shapiro-Wilk test and histograms were used for tests of normality. Median age was calculated for both RTT and TD groups. A Pearson correlation test was performed to determine the correlation between age and attention in calibration, SP, saccades, OKN and torsion swing. The relationship between age and the outcome of the quality of signals was determined by a linear regression analysis. Medians were calculated for percentage looking time of each of the tests. To compare the RTT group and control group, the Mann-Whitney U-test was used for attention and Fisher's exact test was used for signals. A significance level of 0.05 was chosen to detect significant differences within and across groups.

Results

Participants

Seventeen girls and young women with a clinical diagnosis of RTT (median age 7.67 years; range 2.58-25.92; SD 6.636) were included in this second stage evaluation. Sixteen TD children (median age 7.125 years; range 3.58-18.58; SD 3.95) were also included.

No significant correlations were found between age and percentage looking time in either the RTT or TD groups for the calibration, saccades, SP, OKN and torsion swing tests. Furthermore, no relationship was found between age and signals in any tests apart from SP in the RTT group, where there was a positive correlation ($p=0.032$ and $B=0.522$).

Number of Tests

Numbers of participants per test are shown in Table 1. Most participants underwent at least one trial of each test; on some occasions a measurement was repeated while on other occasions a test was omitted due to loss of cooperation or compliance from the participant.

Observational Analysis

Observational analysis demonstrated that the challenges in testing the RTT group were mainly associated with poor attention and low quality of electrode signals. Poor attention

was demonstrated by a low percentage of time looking at the wall. The low quality of electrode signals was illustrated by a high degree of drift. It was decided to quantify these findings.

Table 1. Time spent looking at the stimulus.

Group	Measurement	Time spend looking at the stimulus (%)					Median looking time (%) [IQR]	Total (N)
		0%	1-25%	26-50%	51-75%	>75%		
		% (N)	% (N)	% (N)	% (N)	% (N)		
RTT <i>n=17</i>	Calibration	12 (2) ¹	35 (6)	24 (4)	-	29 (5)	35 ² [63]	17 ³
	Smooth pursuit	24 (4)	6 (1)	24 (4)	18 (3)	29 (5)	50 [83]	17
	Saccades	25 (4)	25 (4)	19 (3)	6 (1)	25 (4)	27 [74]	16
	OKN	6 (1)	19 (3)	6 (1)	35 (6)	35 (6)	70 [62]	17
	Torsion swing	8 (1)	-	17 (2)	17 (2)	58 (7)	87 [50]	12
TD <i>n=16</i>	Calibration	-	-	-	25 (4)	75 (12)	89 [16]	16
	Smooth pursuit	-	6 (1)	6 (1)	25 (4)	63 (10)	91 [30]	16
	Saccades	-	-	-	7 (1)	93 (14)	89 [9]	15
	OKN	-	-	-	-	100 (16)	100 [0]	16
	Torsion swing			6 (1)	13 (2)	81(13)	100 [12]	16

RTT=Rett syndrome, TD=Typically developing, IQR=interquartile range.

¹Percentage (%) and number of individuals (N) in each group within specified bandwidth.

²Median time spent looking at the stimulus, per group per test.

³Total number of participants per test.

Attention

Table 1 shows the quality of attention (in percentage looking time) across the different tests. The number of individuals and percentage of each group falling within each band is shown. A wide distribution for the RTT group is illustrated, while the TD group is largely represented in the top 2 bands (above 50% looking time). Fig. 1 presents more clearly the levels of attention between the groups. A higher percentage looking time in the TD group was found compared to the RTT group for calibration ($p=0.001$, $U=50.00$), SP ($p=0.017$, $U=73.50$), saccades ($p<0.001$, $U=32.50$) and OKN ($p<0.001$, $U=48.00$). No significant difference was found for torsion swing ($p=0.144$, $U=71.50$).

Signals

Tables 2 and 3 show the quality of the signals across the different tests, according to the degrees of drift. It is shown that the majority of trials for the RTT group were

unquantifiable, while all results for the TD group were quantifiable, except for one outlier. Fig. 2 illustrates more clearly the comparison in quality of signals between the two groups. A statistically significant effect in quality between the RTT and TD group was found for calibration ($p<0.001$), SP ($p<0.001$), saccades ($p<0.001$), OKN ($p<0.001$) and torsion swing ($p=0.004$).

Table 2. Quality of signals defined by the degrees of drift for calibration, smooth pursuit and saccades.

Group	Measurement	Classification of quality			Total (N)
		Unquantifiable	Quantifiable		
		>5°/s	2-5°/s	<2°/s	
		% (N)	% (N)	% (N)	
RTT n=17	Calibration	65 (11) ¹	24 (4)	12 (2)	17
	Smooth pursuit	65 (11)	24 (4)	12 (2)	17
	Saccades	50 (8)	38 (6)	13 (2)	16
TD n=16	Calibration	-	19 (3)	82 (13)	16
	Smooth pursuit	-	32 (5)	69 (11)	16
	Saccades	-	13 (2)	87(13)	15

¹Percentage (%) and number of individuals (N) in each group by degrees of drift

Table 3. Quality of signals defined by the degrees of drift for OKN and torsion swing.

Group	Measurement	Classification of quality		Total (N)
		Unquantifiable	Quantifiable	
		>5°/s	<5°/s	
		% (N)	% (N)	
RTT <i>n=17</i>	OKN	60 (9) ¹	40 (6)	15
	Torsion swing	82 (8)	18 (2)	10
TD <i>n=16</i>	OKN	-	100 (16)	16
	Torsion swing	6 (1)	94 (15)	16

¹Percentage (%) and number of individuals (N) in each group by degrees of drift

Figure 2. Quality of signals defined by drift for calibration, smooth pursuit, saccades, OKN and torsion swing. Results for the RTT group are presented on the left of each figure, results for the TD group are on the right

Figure 1. Quality of attention defined by percentage looking time for calibration, smooth pursuit, saccades, OKN and torsion swing. Results for the RTT group are presented on the left of each figure, results for the TD group are on the right

Discussion

The evaluation reported here was designed as the second stage of a two-part study assessing oculomotor function in individuals with RTT [12], after the first stage of assessment led to difficulties with the quantitative analysis of ENG results in individuals with RTT. Two main challenges were encountered: lack of attention and suboptimal electrode signals. Significantly more of these challenges were evident in the RTT group than in the TD group for all tests except torsion swing. It is hypothesized that the RTT group's higher quality of attention on the torsion swing can be explained by the more forceful vestibular rather than visual-ocular stimulus operating in this test. These challenges imply that regular oculomotor examination should be adjusted further to the needs of individuals with RTT.

Quality of Attention

In recent years, several studies have shown that individuals with RTT have difficulty with both selective and sustained attention [16-20]. In order to counteract this, the ENG examination had already been adjusted to a certain extent. Firstly, tests were conducted more rapidly than usual, in order to reduce any loss of attention which might result from a sustained period of testing. Secondly, the examinations were performed in a minimally distracting environment: the room was dark and the technician and the parents were instructed to communicate as little as possible with each other and with the child [25]. Thirdly, the social preference noted in individuals with RTT was taken into consideration by utilizing portrait photographs of family members as stimuli during calibrations, saccadic and SP tests [9, 21, 26]. Nevertheless, attention remained an issue. One reason for poor attention could be related to the fact that the attention pathways are located in the frontal and parietal lobes. Since a significant decrease in the dendritic territories and afferent axons in the frontal cortices have been found in post-mortem brains of individuals with RTT, this could be part of the explanation [27-29]. In addition, anxiety and breathing irregularities are known to be major symptoms of RTT [30, 31]. The unfamiliar situation associated with the examination, the darkened room, and episodes of hyperventilation and breath-holding during testing all appeared, on observation, to be factors interfering with the examination. A lack of interest/motivation in looking at the repeated stimulus may also have played a role. The photographs were small when projected onto the wall, and only 2-3 different photographs were used throughout the testing. The photographs could not be enlarged as it was necessary to stay focused on a specific point. From clinical observation, a better response was seen when a new and novel picture was introduced. This accords with the finding reported by Djukic et al., whereby individuals with RTT exhibited a preference for novel stimuli over a stimulus they had previously seen [32].

Quality of Signals

The other major challenge explored in this study was the quality of the signals. A drift of 5°/s or larger was deemed unquantifiable as normally-measured registrations of eye movements start at 5°/s [23]. Consequently, differentiation between a real eye movement and signal ‘noise’ is unreliable at or above this degree of drift. Amongst other things, poor signals were seen to be caused by poor head control and extraneous body movements relating to the dystonia and ataxia associated with RTT. While testing, a steady, fixed body position is necessary. Every movement, not just eye movements, is registered. In addition, it is hypothesized that the signals could have been better with more time. Achieving a good fixation of the electrodes and allowing time for them to set before they can be used for examination usually takes a couple of minutes. Placement was done more quickly with the RTT participants. After fixation, a poor calibration could also have been due to speed of testing, with faster and shorter episodes of testing leading to inaccuracy. Finally, it should be considered that the corneo-retinal potential of individuals with RTT may differ from other children/adults. Decreased neuronal function may result in a decreased corneo-retinal potential with decreased vision. Reports to date show no significant differences in *MECP2* levels or distribution in the eyes of patients with RTT [33] and no significant abnormalities in brainstem visual evoked potential (VEP) have been identified in studies of the innervation of the eyes [34-36]. However, the role of *MECP2* in the ocular pathway may be an area for further investigation.

Limitations

Analysis showed a variation in results, predominantly in the RTT group. This could be caused by a number of factors, including:

- (i) The broad range of ages (2.58-25.92 for RTT and 3.58-18.58 for TD). Dividing into age groups was considered, but, due to the small sample size, this was not pursued as linear regression models showed that age had no statistically significant effect on test outcomes.
- (ii) The different styles of digital image presented to each group during tests of SP and saccades – cartoon faces for the TD group (standard test presentation) and faces of close family members for the RTT cohort (adapted presentation). Both groups were exposed to the same images of animals for the test of OKN. As described above the use of adapted images for the RTT cohort was an attempt to appeal to their known social preference. However, in future assessments it would be better to use the same media across the two groups in order to remove another potential variable.
- (iii) The different lengths of time the testing took. The selected time-span was determined for each individual by the assessing technician, based on the calibration and the individual’s reaction at the start of the test. In normal circumstances, only a couple of cycles are needed to obtain a good overview and get a reliable result. Consequently, length of testing could be short if the start was good. In contrast, an absent response may have been recorded in

the first trial, while a second trial with the same individual yielded a high percentage looking time. In such cases the absence of a response in the first trial could be due to the known delay caused by a-/dyspraxia in individuals with RTT [37, 38]. Since all trial results were combined, the median percentage looking time was calculated per measurement. A delayed response could thus have interfered with the median percentage looking time.

(iv) Differing levels of visual acuity, which was not assessed. This is not routinely assessed during ENG as the test stimuli are considered to be of sufficient intensity and contrast to allow participants with reduced visual acuity to see and respond to the target. Participants are also permitted to wear their glasses during testing.

(v) The effects of any breathing irregularities (e.g. hyperventilation and breath-holding) during testing. These were not systematically examined but would be a beneficial aspect to explore in the future.

Suggestions for Future Research

One simple suggestion for the immediate future, to achieve both better attention and better signals, would be to use fewer electrodes. From clinical experience, it is known that it is possible for the same ENG testing to be conducted with 3 electrodes rather than 9. In this case, two electrodes are temporal, since electrode fixation is better temporal than nasal, and one on the forehead serves as the earth or reference. Examination of vertical movement is no longer possible, but eye blinks, for example, can be identified by trained clinicians even in horizontal registrations. Secondly, the preference expressed by individuals with RTT for male caregivers, which is noted by some researchers [37], could be exploited in the examinations, by making sure only photos of familiar males are presented. This was trialed in some of the test cases, but was not structurally documented. A third option for examination could be simple observational testing of saccades, SP and OKN. The problems with the signals would thus be eliminated because ENG testing with electrodes would not be required. Observational testing was performed successfully with the TD group. An informal trial with one of the RTT group proved unsuccessful in a normal environment, however, this could be tested more formally with the RTT group in a distraction-free test environment. A fourth suggestion would be to project the images onto a computer screen immediately in front of the test subject, rather than onto a wall, bringing the images closer and in more immediate focus. In this case, however, the image would need to remain far enough away to prevent convergence. A fifth suggestion would be the use of virtual reality (VR) glasses. Through VR a more forceful stimulus is presented, as looking away is not an option. With these glasses, it is also possible to introduce stimuli which may be more appealing. However, the test subject would need to tolerate the glasses and the highly unusual environment, in addition to which using ENG to record the eye movements would mean that the issue of signal quality remains. Therefore, a sixth suggestion would be to use eye tracking glasses instead of electrodes. Virtual reality glasses

combined with an eye tracker may thus be the final solution. This would potentially address both the attention and signal problems but would still require the test subject to tolerate the glasses. Currently such technology is under development and not widely available. For this reason, it is recommended that the other options suggested here are tried first. In the future, however, combined glasses could provide the ultimate solution for accurately examining oculomotor function in individuals with RTT if other ways continue to prove challenging.

Conclusion

A significantly reduced level of attention and suboptimal electrode signals were evident in the RTT group when compared with the TD group for all tests except torsion swing. It is hypothesized that the RTT group's higher quality of attention on the torsion swing can be explained by the more forceful vestibular rather than visual-ocular stimulus operating in this test. Overall, these challenges confirm that regular oculomotor examination should be adjusted further to meet the needs of patients with RTT. Possible solutions and adaptations are suggested.

Acknowledgements

We thank the individuals and families who participated in this study. We also gratefully acknowledge Laura Wagter, for her help in testing the control group, Monique Hiemstra for her help with assessment of the RTT group, and Ellen Rikers for her help with the data analysis.

Declarations of Interest

None

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Chapter 9

Eye Gaze Technology as a Form of Augmentative and Alternative Communication for Individuals with Rett Syndrome: Experiences of Families in the Netherlands

Published as:

Townend, G.S., Marschik, P.B., Smeets, E., van de Berg, R., van den Berg, M., & Curfs, L.M.G. (2016). Eye Gaze Technology as a Form of Augmentative and Alternative Communication for Individuals with Rett Syndrome: Experiences of Families in The Netherlands. *Journal of Developmental and Physical Disabilities*, 28, 101-112.
doi:10.1007/s10882-015-9455-z.

Abstract

This paper provides a brief report on families' experiences of eye gaze technology as one form of augmentative and alternative communication (AAC) for individuals with Rett syndrome (RTT), and the advice, training and support they receive in relation to this. An online survey exploring communication and AAC was circulated to 190 Dutch families; of the 67 questionnaires that were returned, 63 had answered questions relating to eye gaze technology. These 63 were analysed according to parameters including: experiences during trial periods and longer-term use; expert knowledge, advice and support; funding; communicative progress; and family satisfaction. 20 respondents were using or had previous experience of using an eye gaze system at the time of the survey, 28 of those with no prior experience wanted to try a system in the future. Following a trial period, 11 systems had been funded through health insurance for long-term use and two families had decided a system was not appropriate for them. Levels of support during trials and following long-term provision varied. Despite frustrations with the technology, satisfaction with the systems was higher than satisfaction with the support. The majority of families reported progress in their child's skills with longer term use. These findings suggest that although eye gaze technologies offer potential to individuals with RTT and their families, greater input from suppliers and knowledgeable AAC professionals is essential for individuals and families to benefit maximally. Higher levels of training and support should be part of the 'package' when an eye gaze system is provided.

Keywords

Rett syndrome; Communication; Eye gaze technology; Eye tracking; Augmentative and alternative communication (AAC); Support and training.

Introduction

The use of eye gaze or eye tracking technologies to support and facilitate communication with individuals with Rett syndrome (RTT) has been increasingly promoted in recent years [1-3]. It is fair to say it is the current ‘hot topic’ for many families within the global Rett community. Many parents have reported anecdotally over many years that their children with RTT understand more than they are able to demonstrate on assessment or are able to express for themselves, primarily as a consequence of apraxia [4, 5]. This view can sometimes be at odds with professionals who consider that language and cognitive factors also have a role to play. Interest in and a desire to own and use high-tech eye gaze systems is escalating yet the costs are high.

RTT is a rare neurodevelopmental disorder found predominantly in females, characterised by stages of stagnation, regression and (possible) recovery in skills following seemingly near-normal development in the early years of life. A number of authors have written about the staging processes and ages at which they most commonly arise [6-9]. Of particular significance to this study is the propensity for individuals with RTT to engage in “intense eye communication” [10, p. 946]. Other prominent signs contributing to the profile of RTT are stereotypic hand wringing/clapping movements and abnormal gait or an inability to walk. Diagnosis of RTT is primarily clinical, based on the presence or absence of criteria which were revised in 2010 by members of the RettSearch consortium [10]. Following clinical identification, the diagnosis may then be confirmed by genetic analysis which, in the majority of cases, is attributed to mutations in the Methyl-CpG-binding protein 2 (*MECP2*) [11, 12].

Individuals with RTT demonstrate severe limitations in their ability to communicate through conventional channels such as speech and hand signs/gestures [13], due in (large) part to the influence of apraxia or an inability to control purposeful, voluntary movement [1]. In recent years a number of studies have sought to probe deeper into the communicative behaviours of individuals with RTT, to explore levels of underlying intentionality and the range of functions as well as the means by which they are able to express themselves [e.g., 4, 5, 14-18]. In general, the findings of these studies suggest that the majority of individuals with RTT communicate at levels labelled as pre-linguistic and/or pre-intentional. However, it may be more appropriate to refer to the restricted range of socio-communicative functions, where behaviours are interpreted by caregivers and communication partners, as ‘potential communicative acts’ [18, 19]. Such behaviours include the use of stereotyped hand movements, facial expressions, body movements, (undifferentiated) vocalisations, eye gaze and even hyperventilation, and are commonly acknowledged to be in order to seek attention, protest, request or make a choice. Several studies also point to apparently low levels of language comprehension and cognitive functioning [20], especially when standardised receptive language, IQ or adaptive behaviour tests are employed. Two useful overviews of such studies are given by Demeter

[21] and Sigafoos et al. [22]; both reviews point out the problems associated with reliably assessing individuals with RTT and highlight the need for functional tests which balance observational and standardised measures and which ultimately provide a “gold standard” for assessment [22, p.698].

One of the universal features of the above-mentioned studies into communicative ability is the reported use of eye gaze as the most frequent form of expressive communication. Some authors note that eye gaze may simply amount to fixating on an object, raising the question of whether individuals with RTT can use true referential eye gaze, switching between a desired object and a partner [4, 13]. Hetzroni & Rubin [16] were able to show that this behaviour can be trained in individuals with RTT. Other studies exploring cognitive performance through the use of more advanced eye tracking technologies have produced mixed results. For example, the study by Baptista et al. [23] demonstrated that children with RTT could follow key word instructions, recognise and match picture pairs, and categorise pictures. However, a later study was unable to prove the recognition of concepts of size, colour, shape and position [24]. Undeterred by this ‘failure’, a number of more recent studies [1, 25-27] have fuelled interest in the potential benefits that eye tracking technologies can offer to individuals with RTT and have led to calls for the development of more objective eye tracking-based cognitive and receptive language assessments which can be used to validate data gathered from parental reports [5, 28].

Eye trackers measure the “Pupil Centre Corneal Reflection (PCCR)” [29] using a camera to detect the reflection of near infra-red light on the cornea and pupil of each eye in order to determine where the eye gaze is directed. Eye tracking control is potentially life-changing for individuals with severe physical disabilities who are unable to control a computer through more conventional means such as a mouse or keyboard or are unable to utilise other high-tech voice output communication aids (VOCAs) which require access through touch, for example, via a switch or touchscreen. When combined with speech output, eye tracking technology can give users a ‘voice’. For such an application an intact oculomotor system is required. ‘Saccades’, ‘fixation’ and ‘smooth pursuit’ [29, 30] are crucial for purposeful use of eye gaze/tracking technologies. To date, most of the literature published on this technology as a form of AAC relates to use with client groups other than RTT, such as those with Amyotrophic Lateral Sclerosis. Researchers such as Djukic [1, 25, 26] and Rose [27] are beginning to publish about the applied use of eye tracking research in relation to RTT and literature promoting the use of, or sharing experiences of using, eye gaze/tracking technologies for intervention, for developing communication skills and/or facilitating day to day communication in RTT is just beginning to emerge [2, 3, 31, 32]. However, most reports are anecdotal and shared by families and professionals through social media, workshops and seminars or webinars. Therefore, it seems appropriate to ask questions and to plan for the time ahead. To what extent are such systems being taken up and what are the factors that come into play when doing so? What support needs do families have and are those needs being met? If they are not, how can they be met in the future? These

questions are the focus of this study, utilising the Dutch Rett community as a single population case study.

This research focuses on the use of eye gaze/tracking technology from the perspective of families. Research questions are:

1. Are families of individuals with RTT using eye gaze technology to enhance communication? If so,
2. What are the families' support needs in relation to this and how well are they being met?
3. Do families see progress in their child's communication skills?
4. What implications for future service delivery and support for communication can be drawn from families' experiences to date?

Method

Participants and Survey Tool

During the summer of 2014, all 190 families on the mailing list of the Nederlandse Rett Syndroom Vereniging (NRSV, Dutch Rett Syndrome Parent Association) were invited to participate in an online survey relating to communication skills and families' experiences of communication support. The survey was developed by the Rett Expertise Centre Maastricht using Qualtrics online survey software as the host-platform¹. Embedded within the broad survey was a special focus on eye gaze technology.

Analysis

The survey responses were subjected to multi-variant qualitative analysis using the statistical analysis and data reporting tools contained within the Qualtrics software. The results are presented as descriptive statistics. It should be noted that the number of individuals responding to each question was not consistent; no questions were compulsory and individuals could choose not to answer a question if they wished. Thus, not all respondents answered all questions that were open to them.

Results

Sixty-seven out of 190 families completed and returned a questionnaire (return rate = 35%), representing individuals with RTT ranging in age from 3 years 6 months to 60 years 6 months. 63/67 families responded to the questions asking whether their child used now, or had used in the past, an eye gaze system. 20/63 (age range 3 years to 18 years 6 months) reported experience of using a system and 43/63 had never used one.

¹ See <http://www.qualtrics.com/>

Trial Periods, Applications for Funding and Provision of an Eye Gaze System

Of the 20 children with experience, 19/20 were currently involved in a trial or had previously had a trial period with an eye gaze system. Only 1/20 had long-term access to an eye gaze system in school without having had a previous (short-term) trial. Duration of trial periods varied greatly, with the shortest being one week (1/19) and the longest more than three months (2/19). The majority were for 4 (12/19) or 6-8 weeks (3/19). One was of unspecified duration. There was a pretty even split between settings in which trials took place with 7/19 at home only, 7/19 at school only and 5/19 across both settings. Data regarding the levels of support provided during the trials, and by whom, are shown in Fig. 1. The most common form of support reported was that of the supplier offering an introductory session to demonstrate how the system worked and/or to programme the device. Where there was Speech & Language Therapy (SLT) input, alone or with another professional, this usually took the form of one or two sessions in school each week (further details on what constituted a 'session' were not given).

Figure 1. Support during trial periods ($n=19$)

5/19 children were engaged in a trial at the time of the survey. Of the 14/19 whose trial had ended, 12/14 families had submitted a request for funding of a system to their health care insurer while 2/14 had decided that an eye gaze system was not appropriate as their child was too mobile or suffered from too many seizures. One family was still awaiting a decision on their application but the remaining 11/12 requests had been honoured in full.

Of the 43 families who had not yet tried an eye gaze device, 28/43 expressed a desire to arrange a trial period in the near future; 23/28 of these individuals were under the age of 25. Of the 13/43 who were not interested in trialling eye gaze technology, 10/13 were over the age of 25. 2/43 families did not say whether they wanted a trial.

Long-Term Experiences of Using an Eye Gaze System (Post-Provision)

In total, 12 children had access to an eye gaze system for long-term use, 7/12 had been using theirs for 6-12 months, 3/12 for 3-6 months, 1/12 for less than a month and 1/12 for more than a year. The settings in which each child was using their system, the availability of the device and how independent the child was reported to be in using it are shown in Fig. 2. The range of people with whom each child used their system reflected the settings in which the systems were being used, that is, with family members, therapists, teachers/caregivers and other familiar people. The devices were more likely to be available throughout the day at home than at school, and were mounted on a wheelchair, table, or wall in the case of a child who was ambulatory.

Figure 2. Setting, availability of device and independence with long-term use ($n=12$)

11/12 families shared information on the reasons for which their child used their eye gaze system (for example, the communicative functions they conveyed) and the type of page-sets used. Most children used custom-made page-sets with a combination of photos and graphic symbols (8/11), although 1/11 reported using custom-made pages with photos only and 1/11 with graphic symbols only while 1/11 used a combination of custom-made and pre-designed ('off-the-shelf') page-sets with both photos and symbols. All children used their devices for more than one reason, for example, to engage in cause and effect games and to make choices, as illustrated in Fig. 3.

Reports of ongoing support varied. Of the 9 families who answered questions relating to post-provision support, 4/9 received one or two home visits from the supplier to set up the device/train them in its use when it was first delivered, 4/9 received (varying amounts of) support from an SLT and/or class teacher in school or day centre and 1/9 employed an SLT to work with their child at home. When it came to programming devices and adapting vocabulary/adding words so that it was appropriate for the child's needs, 9/9 parents reported that they themselves were responsible for this, although carers within school gave some support in one case.

Figure 3. Reasons for use/communicative functions ($n=11$)

Progress

Eleven families responded to questions relating to progress in communication skills. 10/11 felt that they could see progress in their child's levels of awareness and engagement and their ability to express themselves since having an eye gaze system. They also reported an (apparently) increased understanding of language. One parent qualified this by saying that progress was slow; only 1/11 claimed to see no progress at all.

Family Satisfaction

Family satisfaction was explored across three domains: with support during the trial period, with support for long-term use (post-provision) and with the technology itself. The levels of satisfaction can be seen in Fig. 4.

Figure 4. Satisfaction with support during trial period and long-term use, and with the device ($n=variable$)

When asked what could be improved across the whole trajectory, responses included: more 'hands-on' and intensive support from the supplier, both with planning and

preparation before and during trial periods and with long-term provision; longer trial periods and trials of a greater range of devices/systems; increased knowledge and understanding of how to use the technology among therapists and other professionals, such that they could provide a higher level of support to the child and to the family; and (low-budget) training workshops for families. Technical improvements such as a faster processor and more reliable hardware were also requested. In addition, respondents recognised the value of self-help group(s) and network(s) and requested that a joint position statement be issued by the national parent association and Rett Expertise Centre setting out optimal levels of support recommended to maximise use of, and benefit from, an eye gaze system.

Discussion and Conclusion

The results of the Dutch survey offer some insight into how eye gaze technologies are beginning to be used within the Rett community. There were some frustrations with the technology itself but, on the whole, families who had experience of an eye gaze system reported that they were happy with it, could see progress in their child's skills (depending upon the length of time they had had a device) and were very positive about the potential offered.

Although the numbers of families who reported on their experiences of the technology at the time of the survey were relatively small, it is worth noting that since the survey many of the families who expressed a wish to trial an eye gaze system have indeed done so and the number of families submitting applications to their health care insurer and subsequently provided with a system for long term use has grown substantially. It is no longer the case, however, that all requests are honoured by insurance companies and subsequent to the survey more questions are being raised by insurers about the potential of individuals with RTT to benefit in the face of the high cost of eye gaze technology. This highlights the need articulated in this and other studies [e.g., 33] for well-conducted, well-supported trials over a longer period of time, or even the creation of technology loan banks from which expensive equipment can be loaned and recycled/exchanged more easily if it proves to be inappropriate after a period of well-supported use or as needs and circumstances change. In addition, there is a role for the development of thorough assessment techniques which take into account not only motivational and affective factors and cognitive and receptive language abilities, but also explore the little-researched function of the oculo-motor system in individuals with RTT and the potential effects of apraxia and delayed reaction time on the ability to use eye tracking technology with purpose. Such assessments are especially relevant in cases where an individual is struggling to utilise an eye gaze system effectively, and could contribute to better understanding the mechanisms underlying functional use of eye gaze for communication and help to pinpoint where breakdown may lie.

It is interesting to note the difference between families of individuals under and over the age of 25 expressing interest/disinterest in trialling an eye gaze system. Families were not asked to elaborate further on this preference so underlying reasons can only be speculated, however, this is an issue which could usefully be explored further. By and large, those over 25 lived away from home so families may not have felt able to make a commitment on behalf of carers who were responsible on a daily basis. Yet, informal research in the US and UK indicates that “eye gaze technology is ‘opening up the world’ of communication and literacy learning for individuals with RTT” of all ages [3, p.4], with examples of women aged 29 [3, p.9] and 42 [2] navigating their way to successful communication as soon as they were introduced to a system. Introduction of new technologies in adulthood should not, therefore, automatically be closed.

The levels of training and support offered post-provision, as well as during the trials, were highlighted by families as an important factor modulating successful adoption and use of a device. There is a clear need to build the knowledge and skills of everyone in the individual’s social network if complex communication technology is to be used to maximum effect, i.e. therapists, educators, and other carers as well as close family members. This has been clearly demonstrated by surveys of wider client groups using a diverse range of AAC [34, 35] and the use of eye gaze technology within the RTT population is no exception. This need for skill-building can be fulfilled in a multiplicity of ways. At one level, the sharing of knowledge and advice based on personal experiences can take place informally between parents (and professionals) through social media fora (for example, via Facebook groups) and more formally through the organisation of workshops and seminars during national parent association Family Days. At another level, collaborations between national parent associations from different countries and the development of professional networks within and across countries are important avenues for the dissemination of knowledge, skills and support [36]. At a more individual level, in-depth personalised training and greater hands-on support from suppliers and therapists can be written into the package of care that each family receives with provision of their device. This will naturally carry with it a greater cost. At the current time, within the Netherlands, AAC and therefore eye gaze technology when used to enable communication, falls under the banner of ‘medical equipment’ and is funded by health insurance companies or the AWBZ (Algemene Wet Bijzondere Ziektekosten), a Dutch health law aimed at financing care costs for individuals with long-term chronic illnesses. In certain instances, schools or rehabilitation/day centres may purchase their own devices but these will be institutionally-based rather than assigned to one individual. The source of funding notwithstanding, the principle remains the same: training and support costs should be included within the package cost when a device is supplied to an individual. This may increase the price at face value but will help to ensure better value for money by maximising benefit from the system and reducing abandonment through lack of support [37, 38].

A frustration experienced by families was the time commitment needed to build vocabularies and page-sets within systems, especially as parents were expected to do this. The majority of parents wanted the eye gaze system delivered with a personalised pre-installed vocabulary, with more challenging software included as part of a learning curve, allowing opportunities for practice and helping parents to monitor their child's progress. In other countries (e.g. the UK) greater use is made of a range of commercially-produced page-sets which offer a comprehensive starting point, requiring customisation but involving less work than constructing an entire vocabulary from first principles. In the Netherlands, such pre-designed page-sets are less frequently used, perhaps because fewer are translated into Dutch, and families were certainly keen to see this as a development in the future, especially as the difficulty in building up vocabularies was one of the reasons cited for slow progress. The sharing of pages between families is one simple way in which parents can already offer each other support in this area. This can be at a local/national level amongst members of one parent association, for example, and also at a pan-European or international level through collaborations between parent associations of different countries.

As follow-up to the survey, a number of actions are planned: circulation of a further survey to the speech and language therapists and other AAC professionals named by families, to capture their perceptions, knowledge and experience of eye gaze technology, and the needs they identify; creation of therapist support networks relating to RTT and the use of eye gaze technologies; research into oculomotor movement, apraxia and RTT; and a pilot project to test the validity of a receptive language assessment using eye gaze technology as the form of access.

The findings from the survey represent a small population, with a limited response rate, but nevertheless offer a snapshot of the take-up and use of eye gaze technologies in the Netherlands. Eye gaze (eye tracking) technologies offer potential for individuals with RTT and their families. However, greater input from suppliers and knowledgeable AAC professionals is essential for individuals and families to benefit maximally and the development of oculomotor, cognitive, and receptive language assessments utilising eye gaze technology is crucial to demonstrate, if possible, an individual's underlying and possibly hidden potential.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflicts of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Acknowledgements

The authors wish to thank the Dutch families who participated in the survey, and the NRSV and Stichting Terre-Dutch Rett Syndrome Foundation for their support.

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Chapter 10

International Clinical Guidelines for Management of Communication in Individuals with Rett Syndrome

Submitted as:

Townend, G.S., Bartolotta, T.E., Urbanowicz, A., Wandin, H., & Curfs, L.M.G. (2018).
International clinical guidelines for management of communication in individuals with
Rett syndrome.

Abstract

Difficulties with communication have a profound impact on the lives of individuals with Rett syndrome and their caregivers. Across the world, many families report difficulty accessing appropriate and timely information and services from professionals with expertise in the field of communication and Rett syndrome. To address this need, international guidelines for management of communication in individuals with Rett syndrome were developed by combining available evidence and lived experience with expert consensus. To date, this is the largest project of its kind, developing consensus guidelines for Rett syndrome, with 650 people from 43 countries contributing to the process. A two-stage modified Delphi survey was built on statements and recommendations extracted from systematic reviews of over 300 pieces of literature combined with focus group and survey responses from communication professionals and caregivers. All statements that reached a pre-determined threshold of $\geq 70\%$ agreement were incorporated into the final guidelines; 279 statements were reviewed in Round One and 130 in Round Two. The final guidelines consist of 268 statements and recommendations relating to: rights of the individual; beliefs and attitudes of communication partners; professional knowledge and team work; communication assessment; goal setting; intervention strategies and techniques, including the use of Augmentative and Alternative Communication.

Keywords

Rett syndrome; Clinical guidelines; Evidence-based practice; Expert consensus; Delphi survey; Augmentative and Alternative Communication (AAC).

Introduction

Rett syndrome is a rare neurological disorder known to occur in approximately 1 in 10,000 females across the world [1, 2], and more rarely in males [3]. Core diagnostic criteria include the loss of spoken language and functional hand use [4-7]. Individuals with Rett syndrome experience life-long difficulties with communication; most are nonverbal and some are reported to use augmentative and alternative communication (AAC) systems [8-11]. There is wide variation within and between countries in relation to knowledge and experience of Rett syndrome, and in health, social care and education policies, practices and funding which can lead to discrepancies and inequity in communication services and supports offered [12]. Many families report a struggle to find communication professionals who are knowledgeable and experienced in Rett syndrome and to access the advice, equipment and technological support they need to develop their child's communication [13, 14]. At the same time, communication professionals are challenged to find the information and support they require in order to build their knowledge and expertise in this area [13, 14]. There is a clear need for clinical guidance for parents, caregivers and communication professionals wanting to support the communication development of individuals with Rett syndrome.

Rett syndrome is diagnosed clinically [4], and may be confirmed genetically by identification of a mutation in the methyl-CPG-binding protein 2 (*MECP2*) gene [15]. The first clinical signs are commonly reported as emerging between 6-18 months of age, when parents begin to notice a slowing down in attainment of developmental milestones, followed by a loss or regression in previously acquired gross motor and oral language skills [6, 16]. There is some variation in verbal ability, however; some individuals may develop a small core of single words or phrases prior to regression and retain or add to them post-regression while some individuals may never develop spoken words [17, 18]. Nonetheless, communication skills can continue to develop throughout life [19]. Studies which describe communication skills across the lifespan of individuals with Rett syndrome report the use of multiple modalities to express a broad range of communicative functions with apparent intent, such as making choices, expressing social conventions and needs and wants (pain, discomfort, hunger, thirst), making requests, answering and commenting [8, 11, 20]. Eye gaze is the most commonly reported modality for expressive communication, with various studies recording 80-90% individuals communicating at least some functions through eye gaze [8, 11, 20, 21]. Body movements and the use of AAC devices such as picture boards are the next most common modalities, reported to be used in approximately 50-60% cases [8] while AAC in all its forms is increasingly recognized as a valuable intervention tool throughout life [22]. Gestures are less frequent, reported to be used by 20-45% of individuals [6, 8, 9]. Disturbances in motor movement and planning not only affect the use of gestures but also the timing and consistency of communication; accurate assessment of cognition may be also affected [23-25]. The picture that emerges then is one of complexity

and variability. Co-existing features such as seizures, breathing irregularities, heightened anxiety, fatigue, sleep disturbances, difficulties with sensory regulation, gastro-intestinal problems and scoliosis [4] also impact communication.

Communication partners have an important role to play in accommodating and managing all of these features, in interpreting communicative behaviors [26] and in aiding development of skills [27, 28]. Navigating the literature and identifying appropriate assessment and intervention techniques can, however, be tricky for caregivers and professionals alike and both groups require support, training and enskilling in order to carry out their role [9, 13, 14, 29]. Preliminary evidence suggests that eye gaze technology offers a way for individuals with Rett syndrome to be able to express themselves and to objectively and reliably measure their receptive language and cognition [30-32]. Intervention goals for individuals with Rett syndrome have expanded from establishing basic communication skills (simple choice making and requesting) to facilitating a wider range of communicative behaviors and to developing reading and writing skills [13, 33-38]. This opens up the question of what services, supports and resources are required to ensure individuals with Rett syndrome reach their communicative and educational potential. Globally, there is a lack of clarity in this area and an inequity in knowledge, expertise, service provision and support. Clinical guidelines can help fill this gap. When developed specifically for caregivers and professionals, to provide guidance in specific areas such as communication, clinical guidelines can supplement information available in text books that is often broad, for example, [39, 40], and can complement clinical training in the case of professionals who often do not get in-depth education on specific syndromes. Clinical guidelines have the potential to impact service delivery and to establish a universal baseline, as demonstrated by the consensus guidelines already created to help manage other aspects of Rett syndrome, including scoliosis [41], growth and nutrition [42], and bone health [43].

The overall aim of the current project, therefore, was to develop clinical guidelines for the assessment, intervention and long term management of communication in individuals with Rett syndrome based on available evidence and lived experience combined with expert consensus. The stages of the development of the guidelines and the content of the resulting guidelines will be described in this paper, with a special focus on the Delphi survey which underpinned the consensus process.

Methods

The project comprised three broad phases: systematic reviews of literature; input from parents/caregivers (hereafter described as caregivers) and communication professionals through online surveys and focus group; and, finally, a two-stage Delphi survey to determine expert consensus.

During the project, the research team (the authors) were supported by advice and feedback from an international advisory group of clinicians and researchers with expertise in guidelines development and/or provision of clinical services for Rett syndrome.

Systematic Literature Review

Systematic reviews of published literature were undertaken, with library searches conducted by the first author in April 2016 and repeated in September 2016, April and September 2017, and April 2018 to capture any newly-published articles. The searches were conducted through PubMed/Medline, Psycinfo, Psycarticles, ERIC, and CINAHL, with searches extending to any papers published in the English language which described communication and/or literacy and Rett syndrome. No limits were set for publication dates. The final set of key words utilized in the searches can be seen in Table 1.

Table 1. Published literature search terms and scope.

Participant terms	Communication-related terms	
Rett	Communication	Learning
Rett syndrome	Language	Literacy
Rett disorder	Speech	Reading
	Vocalization	Behavior
	Gesture	Attention
	Understanding	Eye gaze
	Comprehension	Eye tracking
	Cognition	Augmentative and alternative communication
	Cognitive skills	AAC

The titles were filtered according to the predefined criteria and the remaining abstracts independently reviewed by the first and third authors. Any papers which referred to communication and/or literacy in Rett syndrome, at any level of evidence, were accepted. In total, 224 papers met the inclusion criteria. Findings relating to communication assessment or intervention practices were extracted from these papers and compiled in a spreadsheet. Information specifically on communication assessment and intervention in Rett syndrome yielded by the published literature search was, however, limited, so a comprehensive search of other widely available resources, termed ‘gray literature’ was also conducted. Examples of items reviewed included books and book chapters, policy documents, and publications by advocacy groups and parent associations. Information from gray literature was included if it described communication and/or literacy in Rett syndrome or other relevant developmental disability groups. In total, 53 items of gray literature met the inclusion criteria and information concerning communication assessment and intervention was extracted. There were few references (either published or gray) that specifically discussed use of AAC with individuals with Rett syndrome. To fill

this gap, the second and fourth authors reviewed resources on AAC that described strategies mentioned in the published or gray literature searches as being used with at least some individuals with Rett syndrome or provided basic information on use of AAC with individuals with limited or no verbal language. A total of 35 additional resources on AAC were reviewed in this way. The extracted information from the published and gray literature searches was then used to construct a series of statements (simple descriptions or explanations of background status, for example, *“for any individual with Rett syndrome, their level of receptive language (understanding) is usually better than their ability to express themselves”*) and recommendations (obligations or directives to be followed or acted upon, for example, *“AAC should be made available to every individual with Rett syndrome”*) for use in the Delphi survey.

Input from Caregivers and Communication Professionals

Pilot Surveys and Focus Group

Data from real-life experiences of caregivers in receipt of and professionals delivering communication services and support was collected to inform the development of statements and recommendations for use in the Delphi survey. Initial data was gathered at a Rett-specific conference in the United States (US) in 2016. This included a focus group and paper-based surveys that were distributed to attendees, one for caregivers and one for communication professionals. Focus group participants were asked about expectations for communication, tools and strategies used for assessment and intervention, and challenges encountered while working on development of communication skills. The caregivers' survey asked about the individual with Rett syndrome and the services and supports for communication they received, goals set and goals aspired to, strategies, systems and devices used, and any communication-related training caregivers had received. In the professionals' survey, questions related to professional training and experience, work settings, knowledge of AAC and of Rett syndrome, tools, strategies and goals, and factors that contributed to successful communication or posed difficulties/barriers. Ten communication professionals and one individual with Rett syndrome participated in the focus group. Seven professionals' and 19 caregivers' surveys were completed.

Online Surveys

Using data from the focus group and pilot surveys as a basis, two online surveys were developed to collect data from a larger sample of communication professionals and caregivers. Both surveys were run using Qualtrics software, version 2016 (Qualtrics, Provo, UT).

Communication professionals were required to have worked with at least one person (of any age) with Rett syndrome and to be able to respond to the survey in English. They were recruited through social media, specialist Rett syndrome clinics and expertise centers, and

national Rett syndrome associations. This survey asked about professional background, Rett syndrome-related knowledge and experience, Rett syndrome-related service delivery, and eye gaze technology and Rett syndrome. In total, 114 responses were received from 19 countries. Participants included speech and language pathologists (SLPs), occupational therapists, music therapists, and education staff (special education teachers, educational psychologists and educational support workers). Some of the participants further identified themselves as assistive technology (AT) and/or AAC specialists.

The caregivers' survey was open to any caregiver who was able to complete the survey in one of the following 16 languages: Chinese, Danish, Dutch, English, Finnish, French, German, Greek, Hebrew, Italian, Lithuanian, Polish, Portuguese, Russian, Spanish and Swedish. As with the professionals' survey, participants were recruited through social media, specialist Rett syndrome clinics and expertise centers, and national Rett syndrome associations. Questions in this survey asked for basic demographic data (e.g. country of residence, age of person with Rett syndrome, daytime and residential situations), about experiences with communication services and support, exposure to eye gaze technology, and access to information. In total, 490 responses were received, in all 16 languages from individuals living in 39 countries.

Data Analysis

Data from the online surveys were downloaded from Qualtrics into an Excel file; the responses from the pilot surveys were added and the combined data were coded using a content analysis framework [44] with NVivo 11 qualitative data analysis software (QSR International 2015). Information was extracted from the notes taken during the focus group and added to the content analysis. The initial codes were developed by the first author and checked for consistency by the third author; any disagreements were resolved through discussion within the research team. The resulting codes were combined with those extracted from the literature reviews and used to compile the statements and recommendations for use in the Delphi survey.

Modified Delphi Survey

A modified Delphi survey [45] was used to gain consensual feedback on the statements and recommendations, thereby creating guidelines for the assessment, intervention and long term management of communication in Rett syndrome.

Participants

A purposive sampling methodology was employed to identify subject matter experts with significant lived experience of Rett syndrome in either a caregiver or professional role. Caregiver inclusion criteria included having a child (of any age) with Rett syndrome, and diverse experiences as a result of having a wider role in the Rett community e.g., serving on the board of a national parent association, working for a Rett organization. Professional

inclusion criteria included having clinical experience in the field of communication or closely-related area, e.g., SLP, Occupational Therapist, Music Therapist, Educator, Psychologist, and, experience of working with at least 8 individuals with Rett syndrome.

Process

The participants were asked to complete two rounds of an online survey delivered via Qualtrics (see Supplemental Material). In each round they rated statements and recommendations according to a 5-point Likert scale of agreement ('strongly agree', 'agree', 'neither agree nor disagree', 'disagree', 'strongly disagree') or importance ('extremely important', 'very important', 'moderately important', 'slightly important', 'not at all important'). In Round Two a sixth option of 'not my area of expertise' was added following participant feedback in the first round. There were also questions in each round which required participants to rate whether they would use a particular intervention approach with 'all individuals', 'most individuals', 'some individuals' or 'no-one with Rett syndrome', and participants were given the option to write comments beside each of their ratings, or to explain their responses further. Round One also included several open ended questions which aimed to fill gaps in evidence, case scenarios requiring participants to identify goals and strategies, and multiple choice or yes/no questions.

The Round One survey was divided into ten sections: guiding beliefs; features of Rett syndrome that impact communication; team membership, roles and responsibilities, and general principles underpinning support for communication; general strategies to support communication; assessment of general communication skills; AAC assessment; intervention; case scenarios; resources for communication; and, additional considerations for using eye gaze technology. Across the sections there were 279 statements and recommendations to be rated according to level of agreement (n=195) or importance (n=84), 41 questions asking participants to apply the rating of 'all individuals', 'most', 'some' or 'no-one with Rett syndrome', 32 open ended questions, eight case scenarios, and several multiple choice or yes/no questions. Examples of each sort of question are given in Table 2. Participants were also asked to individually rate their agreement on the use of 16 named assessment tools and to suggest how each might be adapted for use with individuals with Rett syndrome.

As in previous guidelines developed for management of scoliosis [41], nutrition and growth [42], and bone health [43] in Rett syndrome, the consensus level for the agreement and importance rating scales was set as a minimum of 70% of responses within one category of the median. Round One rating scale responses were analysed by the third author using IBM SPSS Statistics, version 24 (IBM Corporation, New York) to identify statements and recommendations reaching consensus. Qualitative responses were coded by the fourth author to facilitate the extraction of new information. Based on both forms of analysis, statements and recommendations were constructed for Round Two.

Table 2. Examples of Delphi survey questions.

Type of question/response	Example
Questions requiring a yes/no response	Should there be a maximum time to wait for a response before moving on (e.g., to prevent boredom or loss of interest)? (Yes – No) Please explain why you selected your response above, and if you selected 'Yes' tell us what the maximum wait time should be.
Questions requiring a single response from a multiple choice	When should a low-tech communication system be provided to an individual with Rett syndrome? (please select one answer) (a) As soon as possible after diagnosis (b) When the individual is showing signs of frustration or distress at not being able to communicate (c) Once the individual begins to lose any spoken words they had (d) Other, please specify.
Statements to be rated on the agreement scale	For any individual with Rett syndrome, their level of receptive language (understanding) is usually better than their ability to express themselves. Advice and support for communication should be provided at the moment of diagnosis. AAC should be made available to every individual with Rett syndrome. Eye gaze is not the only way for individuals with Rett syndrome to access AAC.
Question requiring an importance rating	How important is it that caregivers and other communication partners are given information to help them understand how features of Rett syndrome impact communication skills? “Presume competence” is a term that reflects a belief about individuals with Rett syndrome. Please tell us what “presume competence” means to you.
Open ended question requiring a free text response	How would you differentiate between dystonia and dyspraxia/apraxia? Please tell us about any tests or activities you know or any signs you would look for to help distinguish between dystonia and dyspraxia/apraxia, and who should take the lead in making that distinction Which is the more appropriate term to use when describing motor planning disorders in individuals with Rett syndrome – dyspraxia or apraxia? Please explain why you have selected your response above.

The statements and recommendations included in Round Two were those that (i) had not reached a consensus of 70% in Round One; (ii) had reached consensus in Round One but were rephrased or combined to reduce repetition or increase clarity; (iii) were completely new following extra information supplied by participants in Round One; and (iv) were based on intervention goals that had been rated according to ‘all individuals’, ‘most’, ‘some’, ‘no-one’ in Round One and rewritten for the agreement rating scale in Round Two. One hundred and ten statements and recommendations from Round One were combined or reworded for Round Two.

In total, Round Two included 130 statements and recommendations (125 rated according to the agreement scale, five rated for importance) and three questions asking participants to rate whether they would use a particular approach with ‘all individuals’, ‘most’, ‘some’ or ‘no-one with Rett syndrome’. There were no open questions or case scenarios. Round Two rating scale responses were analyzed using SPSS to identify statements and recommendations reaching consensus. Statements and recommendations that achieved consensus as ‘agree’, ‘strongly agree’, ‘extremely important’ or ‘very important’ were included in the final guidelines.

Evidence tables, providing a summary of the supporting literature and study data for each one of the statements or recommendations, were created. The strength of evidence for each statement and recommendation was rated according to the levels of evidence described by the American Speech-Language-Hearing Association [46]. These tables can be requested from the authors.

Results

Delphi Survey

Table 3. Delphi survey participants by role.

Role	n (%) ^a
Speech-language pathologist ^b	13 (29%)
Parent	10 (22%)
Other therapist (occupational, music) ^b	6 (13%)
Rett clinic director/coordinator	5 (11%)
Education staff (teacher educational psychologist, social education worker) ^b	4 (9%)
Researcher (University professor, lecturer)	4 (9%)
Medical doctor	3 (7%)

^aN=36, but several participants reported more than one role.

^bThese categories included individuals who also identified themselves as AT/AAC specialists.

Participants

Sixty eight individuals were invited to participate in the Delphi surveys; 36 agreed. Of these, 21 came from 10 countries within Europe, 11 from the US, three from Australia and one from Israel. Roles of participants were varied, with 29% identifying as an SLP and 22% as a parent (see Table 3). All 36 completed Round One; one participant was unable to take part in Round Two.

Round One Responses

Of the 279 statements and recommendations in Round One, 267 (96%) achieved consensus (see Supplemental Material). For 251 (90%), consensus was at a level of 'strongly agree', 'agree', 'extremely important' or 'very important'. In nine cases the consensus was 'strongly disagree' or 'disagree', in six cases 'neither agree nor disagree', and in one case 'moderately important'.

Some statements and recommendations in Round One were not rated by all participants, meaning that although consensus was achieved this was based on a smaller number of total responses. In particular, those relating to the formal assessments were answered by a small cohort only (ranging from just six to 17 of the participants); of the 16 named assessment tools, eight reached a consensus of 'agree', three of 'disagree', two of 'neither agree nor disagree', and the remaining three fell just below consensus with ratings between 61.6-66.7% for 'neither agree nor disagree'.

Round Two Responses

Of the 130 statements and recommendations in Round Two, 124 (95%) reached consensus (see Supplemental Material). For 115 (86%) this was at levels of 'strongly agree', 'agree', 'extremely important' or 'very important'; for the remaining nine cases (7%), which all related to use of formal assessments, the consensus was 'neither agree nor disagree'.

Questions relating to the three formal assessments that did not reach consensus in Round One were repeated in Round Two, along with eight new assessment tools provided in open text responses by participants in Round One. This time the assessments were grouped into two categories – those for assessing communication skills (n=10) and those for developing and tracking communication goals (n=2). All reached consensus, again based on a smaller cohort of responses (ranging from nine to 15 participants); three reached a consensus of 'agree' and nine of 'neither agree nor disagree'.

Final Guidelines Formulation

In total, 268 statements and recommendations achieved consensus across the two rounds and were included in the guidelines (see Supplemental Material). All those that were included achieved ratings of 'strongly agree', 'agree', 'extremely important', or 'very important'. With the exception of the formal assessment tools, no statements or recommendations achieved a final consensus rating of 'neither agree nor disagree', 'disagree', 'strongly disagree', or 'moderately', 'slightly' or 'not at all important'.

Table 4. Guidelines' section headings and numbers of statements and recommendations according to themes and ratings.

Theme/Section Heading	Total Per Theme	Agreement Ratings					Importance Ratings				
	N=268 ^a	1	2	3	4	5	1	2	3	4	5
Guiding principles (rights, beliefs & attitudes).	20	17	-	-	-	-	3	-	-	-	-
Professional practice (principles of teamwork, responsibilities of professionals, Rett specialist clinics and expertise centers).	29	27	2	-	-	-	-	-	-	-	-
Features of Rett syndrome (and co-existing conditions) that impact communication.	19	7	12	-	-	-	-	-	-	-	-
Strategies to optimize engagement with individuals with Rett Syndrome.	26	8	-	-	-	-	13	5	-	-	-
Assessment of general communication skills (including principles, people & context, procedures & settings).	42	33	9	-	-	-	-	-	-	-	-
AAC assessment (including readiness for AAC, models of best practice, components of assessment).	23	11	12	-	-	-	-	-	-	-	-
Assessment through trials of AAC system/device.	33	10	2	-	-	-	7	14	-	-	-
Intervention (including principles, target setting, techniques).	19	14	5	-	-	-	-	-	-	-	-
Targets and goals for intervention.	57	38	18	-	-	-	1	-	-	-	-
Appendix: Using formal tools for assessment of communication and/or development & tracking of communication goals.	24	-	9	10	3	-	-	-	-	-	-

A=Agreement scale; 1=strongly agree; 2=agree; 3=neither agree nor disagree; 4=disagree; 5=strongly disagree.

I=Importance scale; 1=extremely important; 2=very important; 3=moderately important; 4=slightly important; 5=not at all important.

^aExcluding Appendix.

Table 5. Selected examples of statements and recommendations that reached consensus and are in the final guidelines.

Statement or recommendation	Median Response	n/N (%) ¹
<i>Rights Of The Individual With Rett Syndrome</i>		
In accordance with the UN Convention on the Rights of Persons with Disabilities, all individuals with Rett syndrome have the following rights with regard to communication:		
Right to advice, support and services which start early and continue throughout life.	Strongly agree	35/36 (97.2%)
Right to be offered activities appropriate to their age, interests and culture.	Strongly agree	34/36 (94.4%)
<i>Beliefs And Attitudes</i>		
All communication partners should believe that the individual with Rett syndrome is capable of communicating.	Strongly agree	36/36 (100%)
For any individual with Rett syndrome, their level of receptive language (understanding) is usually better than their ability to express themselves.	Strongly agree	35/36 (97.2%)
<i>Principles Of Teamwork</i>		
Every individual with Rett syndrome should be supported by a multidisciplinary team.	Strongly agree	34/36 (94.4%)
The team should incorporate all significant communication partners and may include the individual with Rett syndrome, their parents/other family members, AAC specialists, SLP, OT, PT, Rett specialist staff, and other key people in the individual's life.	Strongly agree	34/36 (94.4%)
<i>Rett Specialist Clinics And Expertise Centers</i>		
The individual and family may be referred to a Rett Specialist Clinic or Expertise Center in order to get a diagnosis, or for specialized assessment and advice or a second-opinion at any point following diagnosis.	Strongly agree	34/35 (97.1%)
<i>Strategies To Optimize Engagement</i>		
When communicating with individuals with Rett syndrome in any situation, it is extremely important that		

communication partners:

make eye contact with the individual with Rett syndrome.

Extremely important

34/36 (94.4%)

are consistent (in approach, language and vocabulary used).

Extremely important

35/36 (97.2%)

General Principles Of Assessment

Standardized assessments may not accurately reflect an individual's underlying ability nor their communicative and learning potentials but they may be adapted to obtain information on certain specific skills.

Strongly agree

33/34 (97.1%)

Standardized assessments of language and cognition are likely to indicate that individuals with Rett syndrome have an intellectual disability.

Agree

27/31 (87.1%)

Other Considerations For Assessment

Eye gaze is the best access method for assessment of cognition.

Agree

26/33 (78.8%)

Eye gaze is the best access method for assessment of receptive and expressive language skills.

Agree

26/33 (78.8%)

Starting Point – Assessment Of Readiness For AAC

There are no prerequisite skills that must be demonstrated before aided AAC should be considered.

Strongly agree

27/31 (87.1%)

At the time of diagnosis individuals with Rett syndrome should be referred for AAC evaluation.

Strongly agree

26/35 (74.3%)

Trial Periods As Assessment For An AAC System Or Device

Trial periods are essential for assessing whether any AAC system or device is appropriate for an individual.

Strongly agree

34/36 (94.4%)

General Principles Of Intervention

Communication intervention will help to develop functional communication skills, promote cognitive development, provide a foundation for literacy development, and improve social communication.

Strongly agree

34/35 (97.1%)

Communication intervention will help the individual with Rett syndrome to become more autonomous as a communicator. Autonomous refers to an individual being able to communicate what they want to say, to whoever they want to say it, whenever and wherever they want to say it using any form of communication.	Strongly agree	33/34 (97.1%)
Developing Goals For Intervention		
Goals for intervention should include development of nonverbal, low-tech and high-tech strategies.	Strongly agree	31/35 (88.6%)
Targets And Goals For Intervention		
Developing a yes/no response is important for all individuals with Rett syndrome.	Strongly agree	32/35 (91.4%)
Language intervention should begin with exposure to a robust vocabulary (including core and fringe words) so that potential for communication is unlimited.	Strongly agree	26/32 (81.3%)
It is extremely important for an individual to have more than one AAC system or device so that they can be used in different situations/settings (e.g. an eye gaze device indoors and a symbol chart outdoors).	Extremely important	32/36 (88.9%)
Aided AAC can be introduced and used successfully in adulthood.	Strongly agree	30/34 (88.2%)
^a n/N (%)=participants with median response or one category either side.		

The guidelines were ordered under nine headings (see Table 4). Sample extracts of the final statements and recommendations can be seen in Table 5. A handbook containing the guidelines, with the statements and recommendations supplemented by illustrative case scenarios, explanatory texts and links to literature and resources was also compiled for distribution through national Rett syndrome parent associations; a copy of this can be requested from the authors.

Discussion

The project used an evidence based practice model [47] combining research evidence with clinical expertise and caregiver perspectives to develop the first international guidelines for the assessment, intervention and long-term management of communication in individuals with Rett syndrome. This was achieved by consulting multiple sources of evidence and administering a two-stage modified Delphi survey to arrive at guidelines that were evidence-based and verified by consensus. A total of 650 participants from 43 different countries contributed across all stages of the project, representing a variety of roles, and living and working in a variety of contexts. This means the resulting guidelines should be applicable in multiple diverse situations and settings across the world.

Within the guidelines there are sections that are specific to Rett syndrome (for example, relating to the features of Rett syndrome and their impact on communication, the focus on use of eye gaze) and sections that can be seen as more widely applicable to individuals with developmental disabilities and/or communication difficulties. When used by communication professionals, the guidelines are intended to complement or supplement the requirements of mandatory bodies, for example, in relation to continuing professional development for SLPs and other therapists. The guiding principles which outline the rights of the individual with regard to communication and the beliefs and attitudes required of the communication partner set the context within which the rest of the guidelines address what those principles mean in daily life and how they can be achieved in practice. The need to believe in the individual and the importance of being open minded as a communication partner are clearly reflected throughout the guidelines, as is the need to develop and maintain a shared team vision when working with individuals with Rett syndrome. This is especially crucial when seeking to maximize progress and reduce device abandonment [48-50].

Rett specialist clinics and expertise centers can play an important role in offering guidance and support to local teams, although it is recognized that access to such centers will vary greatly within and between countries. The importance of worldwide collaboration is highlighted by the guidelines as is the need to develop models of cross border cooperation and referral. In Europe, the Cross Border Patients' Rights Directive

(2011/24/EU) and the establishment of European Reference Networks such as ITHACA¹, which focuses on rare disorders including Rett syndrome, has opened a potential pathway for referrals to specialist clinics and expertise centers and promotes sharing of professional knowledge and expertise. Families in Europe are eager to see these benefits translated into practice; outside of Europe similar developments should be explored. Where Rett specialist clinics and expertise centers do exist, they should aim to make their services more widely available by offering alternative means of access, for example, through videolink/teleconference. Where such clinics and centres are not currently available, individual clinicians and caregivers can still use the guidelines to help guide and support development of communication with the individual(s) under their charge; they could also use the guidelines as leverage to travel to a city or country providing these services if they have the means to do so. Furthermore, the guidelines also have the potential to be utilized as an instrument with which to lobby local and national governments, for example, to establish specialist clinics and to change policies in relation to funding of services and equipment. The route from research evidence to major shifts in practice is not simple. Policy makers and funders do not quickly or easily change course but guidelines, such as these, with a robust evidence base can offer a solid starting point.

It is clear that Rett syndrome is a complex condition affecting multiple systems and, therefore, the guidelines include specific information on symptoms and features that may impact communication in particular. It is acknowledged that severity of features varies between individuals and may fluctuate and change within an individual throughout the day and across the lifespan. Although a hotly debated area, the guidelines do not specifically differentiate between the effects of apraxia/dyspraxia and dystonia on communication. Both are acknowledged as impacting an individual's ability to respond. Statements are included that reference positive strategies for compensating for motor difficulties or which draw attention to the fact that individuals with Rett syndrome may have a delayed response and which require communication partners to consider how the features of Rett syndrome and any co-existing conditions may impact response time.

Strategies for optimizing communication are also included in the guidelines. These should be followed and put into practice by all communication partners interacting with individuals with Rett syndrome at any time. These are not meant to be confined to 'therapy' situations, but are also intended for daily life. The guidelines offer strategies that can and should be utilized by teachers, therapists and doctors just as much as caregivers and other close family members.

With regard to assessment, it is clear that informal rather than formal methods of assessment are favored, that assessment should be ongoing and dynamic, within natural settings, and that trial of any AAC system by modelling and use over time, rather than trial by testing, is ultimately favored. Recommendations for introducing and implementing AAC

¹ <http://www.ernithaca.org>

also move away from the ‘candidacy model’ [51] which requires individuals to demonstrate prerequisites for AAC before being introduced to any aided (low or high tech) AAC system. This myth has been debunked for many years in the AAC literature [52] and the results of the Delphi survey confirmed that this is no longer the prevailing view among caregivers and communication professionals working with individuals with Rett syndrome, although it is not yet universally accepted. AAC in all its forms is recognized in the guidelines as crucial for development of communication and literacy skills and, in line with widely accepted best practice in AAC [51], it is recommended that AAC should be made available as early as possible and continue throughout life. The guidelines stress that multiple modalities should be used and individuals should have access to both low tech and high tech systems. Individuals do not have to achieve a minimum level of competence with low tech AAC before high tech options can be introduced; neither should they rely only on the high tech. Multiple strategies and forms of communication should be encouraged, while recognizing that eye gaze is likely to be the most reliable form of access, to both low and high tech AAC, for most individuals with Rett syndrome.

Wide-ranging targets and goals for intervention are included in the guidelines, with the ultimate aim being that “communication intervention will help the individual with Rett syndrome to become more autonomous as a communicator”. No claims are made as to the level each individual will reach in their quest for autonomy; it is recognized that each will begin their journey from a different starting point and will finish at a different end point, but the ultimate aim underpinning the guidelines is for all individuals with Rett syndrome be given opportunities to develop their skills and exposed to the conditions which support them to do so.

Strengths and Limitations of the Project

The project aimed to capture information and experience from as many countries as possible and the fact that 650 participants from 43 countries contributed to the various stages makes this the largest project of its kind relating to Rett syndrome. However, the literature searches were restricted to English language documents and the focus group and surveys for communication professionals were available only in English, as was the Delphi survey. Nonetheless 127 different communication professionals from 19 countries contributed to the focus group and/or professionals’ surveys while 36 participants from diverse backgrounds in 13 countries took part in the Delphi process, demonstrating a good spread of data and experience. The surveys for caregivers were translated into 16 languages and reached a wider audience with responses from 39 countries. However, there are still gaps in global coverage.

Overall, the levels of consensus reached for all of the statements and recommendations in Rounds One and Two of the Delphi survey were very high. The nature of the consensus methodology, however, means that there are always likely to be outliers amongst the

respondents and in some cases strong opinions which are expressed at either end of the spectrum may not come through in the final guidelines. It could also be debated whether a 70% cut-off is high enough to safely determine consensus. However, this level is supported by previous research utilizing a consensus methodology to develop guidelines for Rett syndrome [41-43]. It can be regarded as producing a strong guideline, even when there are outliers, as long as there are a sufficient number of respondents and participant recruitment is conducted in a way that minimizes the risk of selection bias, ensures a broad range of views and experiences are represented, and responses are not automatically skewed in a particular direction.

Having only a small number of respondents for some questions could also be seen as a limitation. In the field of rare disorders, however, numbers of potential participants are naturally low and it is a strength of this project that such a large range and number of people were involved across all stages. The only area where responses were particularly low was in relation to the use of formal assessments, which is to be expected, as this is a niche area and availability of assessments will vary according to country and language. As a consequence of the small number of participants familiar with each of the named assessment tools, no specific recommendations relating to their use are included in the guidelines. A number of tools were suggested by participants, along with strategies for modifying them to use with individuals with Rett syndrome. A list of those recommendations and strategies for adaptation is provided as an appendix to the main guidelines; this is intended for information only. A future project could, therefore, usefully gather data on the application of formal assessments to obtain accurate and reliable information on the communication skills of individuals with Rett syndrome.

One final consideration in relation to the Delphi methodology is how statements or recommendations reaching a consensus of 'strongly disagree' or 'disagree' were treated, as this could have required a caution or warning to be issued in the guidelines to steer away from certain techniques or approaches. As described above, any statements and recommendations with a median response of 'strongly disagree' or 'disagree' in Round One were reworded and recirculated in Round Two. Following this, no statements or recommendations achieved a consensus rating of 'strongly disagree' or 'disagree' at the end of Round Two. Therefore, this was not an issue in the final guidelines formulation.

Future Research

Dissemination, implementation and training strategies are being developed in conjunction with different countries, for example, through the creation of professional support and training networks, and translation of the guidelines into different languages. It is envisioned that the publication of the guidelines, rather than being an end point of the research in this area, is a stepping stone towards the development of global evidence based practices in relation to assessment, intervention and management of communication in individuals

with Rett syndrome. Future research will need to focus on implementation and evaluation of the guidelines, especially to ascertain whether they can, in practice, be adapted to suit the health, education and social care policies and practices and funding situations within and between countries. The guidelines will also need to be reviewed and updated as new evidence comes to light. Research is required to develop more appropriate methods for assessing the communication and cognitive skills of individuals with Rett syndrome, methods that adequately recognize the impacts of a multiple system rare disease on communication, cognition, physiological and motor responses. Further research should also be conducted into how appropriate interventions can be applied to ensure communication skills are maximized throughout life.

In developing these guidelines, one individual with Rett syndrome participated in the focus group. This signals a step towards including people with complex communication needs more directly in research relating to their needs and recognizing that they have opinions and experiences that can and should be heard. This should be an important driver for future research.

Conclusion

These evidence-based and consensus-verified guidelines have the potential to improve the assessment, intervention and long-term management of communication in individuals with Rett syndrome, to stimulate training and implementation of best practice across the globe, and to promote research to fill the gaps in the currently limited evidence base. In whatever language and whatever setting they are used, the heart of the guidelines lies in the following statement: “All communication partners should believe that the individual with Rett syndrome is capable of communicating”.

Acknowledgements

The research team wishes to thank everyone who contributed to the focus group and the pilot and online surveys, the members of the advisory group, and the people who gave freely of their time and expertise to contribute to the Delphi survey.

Ethical Approval

Ethics approval for the project was granted by the Ethical Review Committee Psychology and Neuroscience (ERCPN), University of Maastricht, the Netherlands. Specific approval for conducting a focus group and pilot surveys in the US was granted by the IRB at Stockton University, New Jersey, US.

Funding

This work was supported by Rettsyndrome.org under HeART Grant number 3208.

Disclosure of Interest

Financial conflict of interest: This work was supported by a grant to the authors from Rettsyndrome.org.

Non-financial conflict of interest: Theresa Bartolotta has a family member with Rett syndrome. All other authors report no non-financial conflicts of interest.

Supplemental Material

1. Communication Guidelines, Final Statements and Recommendations (including levels of consensus).
2. Delphi Survey, Round One, Questions.
3. Delphi Survey, Round One, Results.
4. Delphi Survey, Round Two, Questions.
5. Delphi Survey, Round Two, Results.

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Chapter 11

General Discussion,
Valorisation and Conclusion

General Discussion

Rett syndrome is a rare disease that is complex and lifelong, affecting multiple body structures, systems, and functions. The Rett research community has come a long way in recognising and understanding the genetic and phenotypic features of the syndrome in the 53 years since the cluster of symptoms was first described by Andreas Rett [1, 2]. Yet, there is much still to find out, much still to understand about the many and various aspects of Rett syndrome. Of particular interest to this thesis are the communication challenges associated with Rett syndrome. These are severe and exert a significant impact on the lives of individuals and their families.

Applied research that seeks to increase our knowledge and understanding of the communication challenges associated with Rett syndrome, and to go some way towards ameliorating them, is crucial if we are to improve quality of life for individuals with Rett syndrome. It is crucial if we are to enable those individuals to communicate in a way that allows their voice¹ to be heard, allows them to be educated and to participate in society. It is crucial if we are to provide the support needed by individuals, their families and professionals working with them. Such applied research was the main focus of this thesis. In order to present a more rounded picture of Rett syndrome in the thesis, the context of Rett syndrome as a rare disease was first outlined and discussed. The context in which the Rett Expertise Centre Netherlands-GKC operates was presented in the form of an overview of the European Union (EU) policy on rare diseases and a synthesis of the transfer of policy into practice across Europe. The second part of the thesis then presented a series of applied research papers, all studies undertaken at the Rett Expertise Centre Netherlands-GKC, relating to various aspects of the communication challenges, needs and potential associated with Rett syndrome.

In this final chapter, the two parts of the thesis are each considered in turn. The main findings from the studies are summarised and discussed chapter by chapter. Included under the umbrella of *“Setting the Context – Rett Syndrome as a Rare Disease”* are the chapters relating to *“Centres of Expertise and European Reference Networks”* and *“Databases and Registries”*. Thereafter, in *“Applied Research Relating to the Communication Challenges, Needs and Potential of Individuals with Rett Syndrome”*, the chapters addressing the three main research aims of the thesis are summarised and discussed, under the headings: *“Increasing Knowledge and Understanding of Aspects of Rett Syndrome, Including Early Development of Communication Skills and Features Underlying Communication”*, *“Investigating the Impact of Communication Needs on Daily/Family Life and the Supports*

¹ The phrase “allows their voice to be heard” recognizes that individuals with Rett syndrome have something to say. Although most will have lost, or never developed, spoken language, the potential and desire to communicate remains within. They are able to express themselves through other, non-verbal, means but these signals may be unclear to others. Augmentative and alternative communication techniques, strategies and systems formalise communication and can enable individuals to ‘speak’ and be heard in society.

Required to Maximise Development of Communication” and, “Developing Guidelines for Management of Communication that Contribute to International Sharing of Good Practice”. Common threads running through all of the chapters are discussed in the **Valorisation** section, together with discussion of the social relevance of the included studies, their implications for clinical practice, policy and decision-making, the potential impact on the lives of individuals with Rett syndrome and their families, and avenues for future research. Finally, there is a **Conclusion** to the thesis.

Setting the Context – Rett Syndrome as a Rare Disease

Centres of Expertise and European Reference Networks

In **Part One** of the thesis, **Chapters Two and Three** set the context for Rett syndrome as a rare disease. As a piece of descriptive work **Chapter Two** provided an overview of rare disease policy and development of initiatives to meet the needs of individuals with rare diseases in the EU, especially those stemming from Directive 2011/24/EU on the Application of Patients’ Rights in Cross-Border Healthcare. **Chapter Three** explored how far, by 2015, policy was being translated into practice for people with Rett syndrome, presenting comparative data from across 30 Member States of the EU and European Economic Area (EEA)². Together the two chapters outlined the legislative requirement for the development of national plans for rare diseases, identification of national, multidisciplinary Centres of Expertise for Rare Diseases, and the sharing of their knowledge and resources through the creation of European Reference Networks for Rare Diseases (ERNs).

Chapter Three presented a synthesis of the situation in Europe relating to Rett syndrome. It showed that, by 2015, all 30 countries had identified at least one centre that was able to provide a diagnostic service for Rett syndrome with a (minimal) level of medical care and advice to families, usually linked to a hospital genetics department. Several European countries already had a nationally-recognised Rett Expertise Centre or, as in the case of Italy and France³, several regional Rett Expertise Centres. In some cases, these centres were embedded within larger multi-disciplinary centres for rare diseases; in other cases, they were single disease centres. The Rett Expertise Centre Netherlands-GKC was offered as one example of a single focus national Reference Centre. Several countries were singled out as hosting their own registry or national database for Rett syndrome while also contributing to larger-scale European or international Rett databases. The value of contributing to such databases was a theme examined in greater detail in **Chapter Four**. Although no ERNs were established at the time of writing **Chapter Three**, this paper highlighted the value to be

² Liechtenstein was not included; neither was Switzerland (within the European Free Trade Association) as neither country was able to supply a contact person or information relating to Rett syndrome.

³ Since this time a new national Centre of Expertise for Rare Diseases, incorporating a national Rett Expertise Centre, has opened at the Hôpital Necker-Enfants Malades in Paris.

gained from pan-European collaborations, with Centres of Expertise and national parent associations both having a central role to play – collaborations, that is, between researchers, clinicians, therapists, educators, parents and ultimately individuals with Rett syndrome. The wishes of parents, as expressed by the national parent associations, were also voiced in **Chapter Three**, and in many ways, these wishes – for early diagnosis, increased understanding of the disease, and better care and support for individuals and families, through dissemination and application of evidence-based knowledge – established the research aims that were addressed in the remaining chapters of the thesis. As added value, **Chapter Three** also presented, in a single table, comparative Rett syndrome demographic data for the 30 included Member States of the EU and EEA, thus making this information easily available to researchers, clinicians, families and interested others at a glance.

According to the most recent annual report produced by RD Action⁴ (August 2018) [3] and the 2018 EU Commission report on the operation of Directive 2011/24/EU [4], 25 of the 28 Member States have now adopted and are implementing and/or evaluating their own national plans for rare diseases. In addition, the first 24 ERNs were launched in 2017, encompassing 900 healthcare units in around 300 hospitals in 25 Member States (plus Norway). Rett syndrome is included in the ERN on Congenital Malformations and Rare Intellectual Disability (ERN ITHACA), that is coordinated by a team in the UK [5]. As outlined in **Chapter One**, there are 350 nationally recognized and government-endorsed Centres of Expertise in the Netherlands at the present time. Dutch Centres of Expertise participate in all existing ERNs and five of the 24 ERNs are coordinated by Dutch Centres. The Expertise Centre for Rare Syndromes and Cognitive Disorders at Maastricht University Medical Centre (MUMC+), which includes the Rett Expertise Centre Netherlands-GKC within its remit, is a member of ERN ITHACA. This offers exciting possibilities for future collaborations between the Rett Expertise Centre Netherlands-GKC and other centres participating in ITHACA.

Databases and Registries

In **Chapter Four** a further aspect of EU policy, that recommending use of rare disease databases and registries as “key instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning” [6], was explored by means of an investigative study. This paper was linked to that of **Chapter Two** where recent advances in genetic testing – next generation sequencing (NGS), including whole exome and/or whole genome sequencing (WES/WGS) – were outlined. Such advances have greatly enhanced the possibilities of accurate (and affordable) genetic diagnosis of rare diseases such as Rett syndrome. As well as highlighting the promise of potential benefit to be gained

⁴ RD Action is an EU Health Programme funded Joint Action (2015-2018), promoting implementation of recommendations on policy, information and data for rare diseases.

from genomic sequencing, however, **Chapter Two** also raised questions of how to interpret causality of (rare) sequence variants, how to act upon ‘incidental findings’ and how to share results among researchers and clinicians, as well as how to communicate these findings to the affected individuals and their families. The study presented in **Chapter Four** provided answers to some of these questions by evaluating a number of genetic and phenotype databases according to FAIR principles (findability, accessibility, interoperability, and reusability) [7]. It also explored user functionality, and type and amount of genetic and phenotype information contained within each database. Using Rett syndrome as an example, 13 databases were identified and searched for five different *MECP2* mutations. In general, the databases and the specific mutations were challenging to find, and database interoperability (a cornerstone of recommendations by EUCERD⁵ [8]) was found to be poorly developed. That said, several thousand online database entries were uncovered for *MECP2* mutations and their associated phenotypes, diagnosis or predicted variants. This demonstrated that there is a solid starting point for researchers and clinicians to provide, annotate and use data that has been gathered and is available in such databases. With the increasing availability of affordable genomic sequencing there is clearly the potential to collect and share more detailed phenotypic descriptions of genetic variations. To be of most use and potential benefit, however, databases must comply with minimal information standards, such as those recommended by EUCERD [8, 9], for example, making clearer use of patient identifiers and common ontologies.

Within **Chapter Four**, rare disease patient registries and population-based, longitudinal or epidemiological databases were not examined in detail. There are increasing numbers of studies attempting to delineate differing profiles of Rett syndrome and its variants according to mutation and/or to define which mutations may predict more or less severe phenotypes of Rett syndrome, some of which utilise data from large scale, longitudinal, population-based databases [10-21]. In the near future, there are also likely to be studies seeking to identify how specific mutations dictate the treatments required or influence the response to those treatments. In these instances, patient registries and longitudinal population-based databases, such as those associated with the Australian Rett Syndrome Study and the US Rett Syndrome Natural History Study can prove invaluable. Indeed, studies seeking to delineate more specific speech-language and communication profiles of individuals with Rett syndrome according to mutation or Rett variant (for example, the preserved speech variant (PSV)) have begun to emerge from these two sources [11, 22] and sit alongside other studies offering speech-language and communication profiles based on smaller samples [e.g. 23, 24].

When considering the array of studies that seek to profile Rett syndrome, its features and their severity according to mutation, it is increasingly evident that the identification of

⁵ EUCERD was the European Union Committee of Experts on Rare Diseases; it was replaced in 2014 by the EC Expert Group on Rare Diseases.

a *MECP2* mutation alone can give a hint of what to expect from the present and future course of the disease for an individual but it does not give sufficient information. The interaction between the mutation and other factors such as x-inactivation, distribution of affected/unaffected cells throughout the body, an individual's genetic background and their environmental influences is immensely complex [21, 25-27]. How, then, can these complex interactions best be analysed so that their implications, their impact on real individuals and real lives, can be translated into practical advice and action? This is where longitudinal population-based databases and patient registries have a special role alongside the genetic and phenotype databases. Well-designed and well-curated databases and registries can make a significant contribution towards improved and earlier diagnosis, research, treatment and management of rare diseases such as Rett syndrome, when populated by good quality, detailed, FAIR data. Centres of Expertise like the Rett Expertise Centre Netherlands-GKC have a key role in contributing to, if not themselves creating and curating, such databases.

Applied Research Relating to the Communication Challenges, Needs and Potential of Individuals with Rett Syndrome

In **Part Two** of the thesis, three applied research aims were addressed relating to aspects of the communication challenges, needs, and potential of individuals with Rett syndrome: (1) to increase knowledge and understanding of aspects of Rett syndrome including early development of communication skills and features underlying communication; (2) to investigate the impact of communication needs on daily/family life and the supports required to maximise development of communication; and, (3) to develop guidelines for the assessment, intervention and long-term management of communication that will benefit individuals with Rett syndrome, their families and professionals working with them, and that contribute to international sharing of good practice. Taken together these aims relate to three components of the World Health Organization's International Classification of Functioning, Disability and Health (ICF) [28], namely body functions and structures, activities and participation, and environmental factors.

Chapters Five to Ten of this thesis aim to contribute towards an understanding of specific aspects of Rett syndrome, and towards addressing questions of need and provision at both individual and group levels. How this was achieved will be discussed by considering each of the aims in turn.

Increasing Knowledge and Understanding of Aspects of Rett Syndrome, Including Early Development of Communication Skills and Features Underlying Communication

Chapter Five was included, not as a piece of applied research, but as a segue between **Parts One and Two** of the thesis. It was invited for inclusion in a new text book (currently the

definitive text book) on Rett syndrome, with chapters authored by leading researchers around the world. This chapter was written as a synthesis of knowledge relating to communication, cognition, and behaviour in individuals with Rett syndrome. Of particular relevance to this thesis is that it described how improved awareness and understanding of the features associated with Rett syndrome have influenced and changed thinking about cognitive potential and early communication development, later communication deficits and skills, and strategies for intervention and management of communication. For example, studies by Marschik et al. [29-33] and others [34-37], have shown that contrary to popular beliefs, the early communication development of individuals later diagnosed with Rett syndrome can show signs of disruption prior to regression. Amongst other things, these studies have identified reductions in early gestural and vocal repertoire, abnormal quality of vocalizations (e.g. produced on an ingressive airstream), failure to reach early milestones such as canonical babbling, and deficits in early socio-communicative behaviours (e.g. joint attention and reciprocity). By considering studies based on large-population samples such as the Australian Rett Syndrome Study and US Natural History Study, as well as smaller-scale parental report, questionnaire, and observation-based studies, **Chapter Five** outlined the variability in spoken language, with some individuals with Rett syndrome developing early single words or phrases that they lose during regression; some who retain their spoken vocabulary, even expanding it after regression (most likely in individuals diagnosed with PSV); and, others who never develop recognisable speech [11, 19, 21, 22, 38, 39]. Yet, as the chapter further outlined, individuals can use multiple modalities to express a wide range of communicative functions, with eye gaze being the most commonly reported modality for expressive communication [40-44]. A number of more recent, exciting AAC intervention studies were also reported in this chapter, as evidence that communication (and literacy) skills can be developed later in life [45-49].

The debate surrounding the relative impact on communicative ability of the movement disorders experienced in Rett syndrome (especially dyspraxia, the inability to control purposeful, voluntary movements) and any possible deeper language and/or cognitive impairments was also discussed in **Chapter Five**. This is a hugely topical debate as Rett syndrome has historically been described by many researchers as one of the leading causes of severe intellectual impairment (in girls/women) [e.g. 50-53], which oftentimes has been (and still is) at odds with parents' reports of their child's understanding. Reviews conducted by Demeter [54] and Byiers [55] were referenced to point out the shortcomings in using traditional-style cognitive and receptive language assessments as measures of ability in Rett syndrome. Studies by Djukic and Rose and colleagues [56-59], among others, were included to show the contribution that eye tracking technology can offer towards a better understanding of (hidden) abilities in Rett syndrome, abilities that are otherwise masked by the impaired ability to give conventional motoric responses. The study by Clarkson et al. [60], in particular, was highlighted as evidence that, given appropriately-modified

assessment tools, individuals with Rett syndrome can demonstrate cognitive abilities ranging from low average to age-equivalent, or can even perform above their age (for example, in the receptive language and visual reception (non-verbal) domains). A subsequent publication by Ahonniska-Assa et al. [61] has also confirmed that, when assessments are modified for use with eye tracking, some individuals with Rett syndrome can demonstrate receptive language scores that are age appropriate. Neither the Clarkson nor the Ahonisska-Assa study claim that all individuals perform at a high level given modified assessments, but what they do illustrate is a greater receptive language and cognitive variability – and potential – in comparison with previous opinion. Thus, it has become clear that identification and deployment of suitably modified tests is vital in understanding and addressing needs appropriately. “Accurate assessment is paramount in understanding the needs of individuals with RTT, which will ultimately result in the development of targeted therapies and interventions to improve their quality of life” [60, p. 429].

Therefore, **Chapter Five** was important in setting the communication context for the applied research chapters that followed; it was important in setting a context underpinned by a belief in the potential of individuals with Rett syndrome, a context that does not see only deficit and inability.

In **Chapter Six** a study conducted in collaboration between the Rett Expertise Centre Netherlands-GKC and iDN @ Göttingen and Graz⁶ was presented. This study was predominantly related to the body functions domain of the ICF, utilizing retrospective video analysis to examine more closely early markers of Rett syndrome focusing on the pre-diagnostic period of life. In this case, the study compared response to name as a marker of social reciprocity in two cohorts of infants aged between 5 and 24 months, one with classic/typical Rett syndrome and one with PSV. From analysis of the everyday recordings made by families before they were aware of their child’s diagnosis, two distinct profiles were revealed. The girls with typical Rett syndrome demonstrated a higher response rate to their name being called at 5 to 8 months which noticeably declined from 9 to 12 months onwards, while those with PSV showed a markedly higher rate and range of responses by the age of two. Through identifying subtle and nuanced differences in one early communication behaviour, this study aimed to contribute both to the body of studies delineating differing socio-communicative profiles in Rett syndrome [29-33], and to those seeking to increase knowledge and awareness of other early markers of Rett syndrome [e.g. 62-64]. According to Einspieler and Marschik, authors of a recent review of similar studies, this is a necessary and important area of research and “The challenging period of pre-regressional development in RTT should receive intensified attention in order for clinicians to delineate disorder-specific signs” [65, p. 330].

⁶ The Research Unit iDN – interdisciplinary Developmental Neuroscience is currently based in the Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Center Göttingen, Germany, and the Department of Phoniatrics, Medical University of Graz, Austria.

At the same, time, however, there are some limitations to the study in **Chapter Six**, which mean the results must be treated with caution. The use of retrospective video analysis is acknowledged to be problematic due to potential contextual differences and lack of consistency between settings and situations, and differences in duration and availability of recordings for participants [66-68] although, in the absence of other options, it yields opportunities for analysis of the pre-diagnostic era that would otherwise be lost. In addition, Einspieler and Marschik point to the difficulty of retrospective studies reliant on small sample sizes: “But how specific are these behavioural deviations to RTT? The lack of comparative studies on larger data sets still makes it impossible to say whether the absence of certain behaviours at a specific age band and/or, even more so, their abnormal quality is unique to RTT or is in fact shared by individuals with other developmental disorders” [65, p. 329]. This may be inferred to apply to the study included in **Chapter Six** as it is focused on a limited sample size, comparing two variants of Rett syndrome, with no control group. Whilst a small sample size does not nullify the findings, these findings naturally become more meaningful if they can be replicated with larger Rett cohorts and/or compared with other subject groups (both typically-developing children and those with other developmental disorders) and work in both of these areas needs to be continued. Larger birth-cohort studies [69, 70] may be helpful in this, although they generally provide an overview of developmental milestones that allows for broad identification of the characteristics of sub-groups within the population, rather than exploring specific aspects of development in greater depth. Alternatively, cross-syndrome review papers can increase the value of small scale studies by enabling comparison of the more detailed aspects of individual studies across differing cohorts. Recently, the study in **Chapter Six** was included in a cross-syndrome review of response to name in the first 24 months of life [71]. By combining a review of 23 published studies with their own retrospective video assessments of response to name in infants later diagnosed with classic and atypical (PSV) Rett syndrome, autism spectrum disorder (ASD), and Fragile X syndrome (FXS), Zhang et al. found that four distinct developmental profiles were apparent, with between-group differences becoming more evident with increasing age. While all infants presented with a lower response to name than their typically developing peers by the age of 12 months, those with FXS were less impaired than those with ASD, and those with classic Rett syndrome were the most severely impaired. Those with PSV fell between the profiles of ASD and FSX. By age two, the differences were maintained and were more pronounced. Inclusion in this comparative review strengthens the findings of the study in **Chapter Six**, and encourages this and similar work to continue in the future in order to build “a comprehensive early detection model characterising age-specific neurofunctional biomarkers associated with specific disorders, and contribute to early identification” [71 p. 95], in this case of Rett syndrome.

Chapters Seven and Eight presented the first and second parts respectively of a two-part study conducted as a collaboration between the Rett Expertise Centre Netherlands-GKC

and the Department of Otorhinolaryngology (ENT) at MUMC+. This study explored the ICF domains of body structures and body functions, further contributing to increased understanding of aspects of Rett syndrome, namely of eye movements that underpin communication through eye gaze. As described in **Chapter Five**, individuals with Rett syndrome are reliant on eye pointing or eye gaze as a primary means of communication, yet the neural and motor pathways associated with this are relatively under-researched. In the first part of the study, the oculomotor movements (horizontal saccades, smooth pursuit (SP), optokinetic nystagmus (OKN), and vestibular-ocular reflex (VOR)) of 18 girls and young women with Rett syndrome were investigated through testing via electronystagmography (ENG), and the results compared with normative data collected from 16 typically-developing children and teenagers. The four movements of interest share the common aim of stabilizing images on the retina (specifically on the fovea), either by holding gaze and image steady (SP, OKN and VOR) or by shifting gaze to bring images to the fovea independent of any head movement (saccades). Fixation (holding an image on the fovea to allow time for visual analysis of the image) was not directly assessed in this study.

The results presented in **Chapter Seven** suggested that the cohort with Rett syndrome appeared to demonstrate intact oculomotor function, with a range of eye movements predominantly on a par with their typically-developing peers. For example, all of the controls and the majority of those with Rett syndrome who gave a measurable result demonstrated SP, saccades, OKN and VOR, with no major differences immediately apparent between the two groups across most of the quantifiable measures. However, there were some points of interest. For example, evidence of a longer saccades latency in the cohort with Rett syndrome (time delay between stimulus and response, i.e. the time taken to shift gaze to an image moving abruptly at random intervals). This accords with work published by Rose et al., who also report increased latency in saccadic eye movements in individuals with Rett syndrome [72-74]. The significance of this increased latency requires further investigation, especially in the context of dyspraxia being a recognised feature of Rett syndrome [75]. Generally, use of the term ‘dyspraxia’ (or ‘apraxia’) in Rett syndrome is associated with gait and hand skills [76-78]. What is not known is whether this can also be applied to their oculomotor/eye movements. On this point, the results of the study in **Chapter Seven** are not conclusive. As testing continues, however, and statistical power can be improved, the answer to this question may become more apparent and may carry implications for the use of eye gaze for communication.

A number of difficulties were also encountered in executing the ENG testing with the Rett cohort that made quantitative analysis problematic. Poor signal to noise ratios interfered with the quality of the recordings, meaning good calibrations were sometimes difficult to achieve and signals were not easy to read. Reduced motivation, interest in and attention to the test materials also appeared to be significant factors. Therefore, in the second part of the study, **Chapter Eight**, these difficulties were analysed in greater detail, and published in a paper described in a journal-commissioned editorial as one that “addresses an

important issue and (that) can be useful to overcome the main problems that researchers have in working with RTT with Eye tracking technology” [79]. This time the ENG results of 17 girls and young women with Rett syndrome were compared with those of 16 typically-developing peers. Of particular interest were (a) quality of attention, which was measured in percentage looking time, and (b) quality of signals, which was measured in degrees of drift. Significant differences were confirmed between the groups, with the Rett cohort demonstrating a lower percentage looking time (reduced attention) across all measures except for VOR, and greater drift (lower quality signals) across all measures when compared with the control group. A number of factors could underlie these differences, relating both to features of Rett syndrome and to features of the assessment situation. Reduced attention may, perhaps, be attributed to the fact that the attention pathways are located in the frontal and parietal lobes of the brain, and decreased dendritic territories and afferent axons have been found in the frontal cortices of post-mortem brains of individuals with Rett syndrome [80-82]. Anxiety and breathing irregularities (both major symptoms of Rett syndrome), especially the hyperventilation and breath-holding that were noted during the testing, may have played a role, provoked by the unfamiliar assessment situation and the darkened room, while a lack of motivation or interest in the visual stimuli may have been related to the small size of the images and their repeated presentation. Poor head control and dystonic body movements (further features of Rett syndrome) are also factors that are likely to have interfered with the registration of the eye movements, exacerbated by poor fixation of the electrodes, due to speeding up the time taken to attach the electrodes to the participants in order to reduce anxiety and discomfort.

Taking these factors into consideration, future assessments of oculomotor function must be adapted to better suit individuals with Rett syndrome, for example, reducing the number of electrodes, utilising more motivating stimuli, making the images larger and bringing them closer, performing observational assessments rather than ENG, and trialling the use of virtual reality (VR) and/or video tracking (VT) glasses. VR glasses would allow for the stimuli to be highly personalised, motivating and close-up, but would require the wearer to tolerate the VR headset as well as the electrodes to register the oculomotor movements; VT glasses would remove the need for the electrodes, as the glasses themselves register the eye movements, but would require external stimuli still to be used. Ideally, technology would be developed in the future to combine these two elements in one set of glasses.

In conducting this oculomotor research, it is recognised that an intact oculomotor system is just one element in a multi-layered set of pre-requisites for purposeful use of eye gaze for communication. Other studies analysing use of eye gaze or eye tracking in individuals with Rett syndrome have considered other parameters, for example, assessing selective attention or evaluating and training joint attention behaviours [56, 57, 72, 73, 83, 84]. The ability to use referential eye gaze or ‘eye pointing’ is a central or key element in the communication process. Sargent et al. [85] offer a useful working definition of eye pointing,

as the “context-relevant, controlled and intentional use of gaze in order to direct one or more partner’s visual attention to any item or object for a deliberate communicative purpose” (p.479). They further suggest that “eye-pointing can be seen as the integrated outcome of a combination of visual, social, cognitive and motor skills” (p. 482). These elements can be further broken down into: an individual’s levels of arousal and alertness, their visual attention skills, visual perception, visual acuity, visual memory, oculomotor function, motivation and desire to communicate, understanding of cause and effect and reciprocity, understanding of the world around them, and levels of receptive language (language comprehension). An indication of intact oculomotor functioning, therefore, cannot be taken on its own as a guarantee that an individual will prove to be a successful and competent communicator via eye pointing or eye gaze. However, it places one piece in a rather complex puzzle. If an individual with Rett syndrome appears to be ‘failing’ or struggling to use eye gaze, or eye tracking technology, for communication, an assessment of their oculomotor system is a starting point for unravelling where the point of breakdown may lie, a starting point that assesses whether an individual is able to maintain and shift fixation of static and moving targets. It is at this level of basic oculomotor skill that the studies in **Chapters Seven and Eight** were aimed. In the future, research should be extended to other elements in the matrix, to build a more rounded and complete picture of the purposeful and functional use of eye gaze for communication. This will then open up opportunities for interventions to be targeted at areas of need in order to establish the conditions upon which successful communication through eye gaze can be built.

Investigating the Impact on Daily/Family Life and the Supports Required to Maximise Development of Communication

In **Chapter Nine**, a qualitative study conducted as a collaboration between the Rett Expertise Centre Netherlands-GKC and the Dutch Rett parent organisations (Nederlandse Rett Syndroom Vereniging (NRSV) and Stichting Terre) was presented. In the study, an online survey was developed to investigate families’ experiences of AAC, and the advice, training and support they received, with a special focus on eye gaze/eye tracking technology. This was in line with the ICF components of activities and participation, and environmental factors as an influence on functioning and disability. Circulated to 190 families, 63 surveys were returned with sections completed in relation to eye tracking technology. When these were analysed, the following parameters were considered: experiences during trial periods and with longer-term use; expert knowledge, advice and support available to families; funding; the child’s communicative progress; and family satisfaction.

Approximately one third of respondents (n=20) were using or had previous experience of using an eye gaze system at the time of the survey, while the majority of those with no prior experience (n=28) hoped to try a system in the future. Following a trial period, a number of systems had been funded through healthcare insurance for long-term use

(n=11) and a small number of families had decided such a system was not appropriate for them/their child (n=2). The length of trials and levels of support during trials and following long-term provision varied. For example, trial periods ranged from one week to three months with the average being four to eight weeks, with support varying from an introductory session with a device supplier to weekly sessions with a speech and language therapist (SLT) in school or at home. All families reported having to build page sets/vocabulary, and to programme the devices themselves. Almost all families who had been provided with a device for long-term use reported seeing progress in their child's levels of awareness and engagement and their ability to express themselves since having an eye gaze system (n=10), even if their rate of progress was slow. Only one did not see any progress. Although expressing some frustrations with the technology, families were generally satisfied with their device. They were not satisfied, however, with the levels of support they received, and the study concluded that while eye gaze technologies offer potential to individuals with Rett syndrome and their families (a facilitating external factor according to the ICF), greater input from suppliers and knowledgeable AAC professionals is essential for them to benefit fully (with the existing low levels of help and support proving an external barrier or hindrance to activities and participation).

One aspect with which families expressed a need for greater help and support was the time and effort required to build up vocabularies and page sets on the device for their child. At the time of the survey there were a number of pre-programmed page set options available in English but very few in other languages, including Dutch. This meant that families in the Netherlands generally received a 'blank' device loaded with the software needed to create their own page sets and vocabularies from scratch, with nothing already set up. In some instances, the supplier might pre-programme a basic vocabulary prior to delivery of a device, based on the family's wishes, and in some instances an SLT might take on the task of adding vocabulary, but in all cases reported in the survey, parents needed to carry this on and develop it further themselves. The time required to do this, and to do this well, was enormous. This left individuals reliant on the time, and thought, their parents/carers could make available and were prepared to invest in the task. In the few years since the survey was undertaken, however, there has been a surge in the field of eye tracking technology, with growth in the range of devices available, growth in the available software and English-language page sets and vocabularies, and growth in the availability of other language page sets including Dutch. Now families are faced with choices, choices of which device, which software and which page set to select for their child, choices that may be wide open or may be limited or dictated by a healthcare insurer or funder. Although this may be a daunting, and sometimes frustrating, set of choices to make, and is an area in which families still value guidance, it is surely a better, time-saving, and more exciting prospect than having no choices at all.

Positive developments in this one area do not, however, negate the need for higher levels of training and support that were identified by the study in **Chapter Nine**. Training and

support for individuals and their families must be factored in and included as standard whenever an eye gaze system is supplied. It is well-documented within other AAC populations that a lack of adequate training and support is one of the factors that can lead to device abandonment [86-88]. Giving a device to an individual is not sufficient on its own. Do members of the family/carers have the technical skills and the knowledge required to set up the device, to position it appropriately, to deal with breakdowns and technical faults, to personalise page sets and vocabulary, to know how to develop and progress an individual's communication skills? Appropriate training and opportunities for regular or ongoing support are essential. Yet, appropriate training and support can only be given if the professionals expected to provide it are also adequately trained and possess the necessary skills and time. Oftentimes, professionals themselves struggle with these elements. SLTs receive minimal AAC training in their undergraduate/pre-clinical education, and are unlikely to be taught anything specific to Rett syndrome; once qualified, they may struggle to access training at more than a cursory level, and may also struggle to allocate the time necessary to provide a high level of support for one individual or one family in the context of their other caseload commitments. Suppliers – although skilled in the technological support aspects – may not possess the clinical skills and are unlikely to have the time to offer ongoing high levels of support to individuals and families. All of this then carries implications for funding and service level organisation – funding for devices is needed but provision of hardware and software without training and support is inadequate. Costs for training and support must be factored in, for professionals as well as individuals and families, and time must be set aside to allow for this. Further, once provided to an individual, funding must be made available on a lifelong basis; how can a device be taken away without being replaced when it breaks down or becomes obsolete? How can an individual's means of communication be taken away once it has been given to them? Innovative solutions that go some way to meeting the training and support needs – such as the development of professional training and support networks, peer mentorship, and creation and deployment of online resources and e-learning platforms – will be discussed in the **Valorisation** section below.

Developing Guidelines for Management of Communication that Contribute to International Sharing of Good Practice

The final research paper presented in the thesis, **Chapter Ten**, exemplified the key role that can be played by Expertise Centre researchers and clinicians in developing international clinical guidelines, guidelines that set a benchmark for good practice and provide structure and guidance for parents and professionals. This project was led by the Rett Expertise Centre Netherlands-GKC, in collaboration with researchers from the US, Australia and Sweden, making a core team of four that was chaired and coordinated by the candidate for this PhD. It was (and is) the largest project of its kind to date, developing consensus guidelines for Rett syndrome, with 650 people from 43 countries contributing to the whole

process. It is also the first project in the world to develop guidelines for the management of communication in Rett syndrome. Like the study above, this related to the ICF components of activities and participation, and environmental factors that influence functioning and disability.

As described throughout this thesis, difficulties with communication have a profound impact on the lives of individuals with Rett syndrome and their families. Despite the growing awareness of rare diseases, globally as well as within Europe, and despite the development of policies and initiatives by bodies such as the EU Commission, WHO and UN as reported in the **Introduction** to this thesis, and **Chapters One – Three**, many families across the world still report difficulties in accessing appropriate and timely information and services from professionals with expertise in the field of communication and Rett syndrome. It was to address this need that the project in **Chapter Ten** was devised, namely to create international guidelines for the assessment, intervention and long-term management of communication in individuals with Rett syndrome. The project combined available evidence and lived experience with expert consensus, beginning with a systematic literature review that resulted in analysis of over 300 pieces of published and grey literature. This was followed by surveys conducted online with communication professionals and parents of individuals with Rett syndrome around the world, yielding data from over 100 communication professionals and almost 500 parents, in the 16 languages in which the survey was made available. Statements and recommendations extracted from the literature reviews and surveys were combined and fed into a two-stage modified Delphi survey involving a smaller invited group of ‘expert’ parents and professionals from around the world (n=36). All statements and recommendations that reached a pre-determined threshold of $\geq 70\%$ agreement were incorporated into the final guidelines. After 279 statements and recommendations had been reviewed in Round One and 130 in Round Two, guidelines were formed from 268 statements and recommendations, grouped according to the following themes: rights of the individual; beliefs and attitudes of communication partners; professional knowledge and team work; communication assessment; goal setting; and, intervention strategies and techniques, including the use of AAC (see Appendix for a copy of the final statements and recommendations).

Many of the recommendations included in the guidelines relate to good professional practice and are intended to be read alongside the mandatory requirements of professional bodies for continuing professional development, particularly where the guidelines set out requirements for a minimal skill set and ongoing training needs for SLTs and other communication professionals; emphasis is placed on team working, with a concept of a ‘communication team’ bringing together parents and professionals in partnership. The role of Rett Expertise Centres and specialist clinics in supporting individuals and families in their own country and through cross-border referrals is highlighted, while AAC practices and techniques that are applicable to a wide range of populations are also recommended. The

use of AAC in all forms is recognised as vital for the development of both communication and literacy skills. Informal methods of assessment are favoured above formal and standardised assessments. Intervention techniques and strategies, and wide-ranging targets and goals for intervention are recommended, not only for use in formal ‘therapy’ sessions but for optimising communication in everyday settings.

The guidelines are unique in bringing together all of these elements and showing how they apply to individuals with Rett syndrome. They also highlight the areas that are unique to Rett syndrome, for example, the impact of breathing irregularities on communication, and the need for communication partners to allow for increased ‘wait time’ when expecting a response from an individual, in recognition of the dyspraxic and dystonic body movements that interfere with and slow down purposeful, voluntary control. One of the key messages the guidelines strive to convey is belief in the individual and their potential. The guidelines are written to be independent of location (country and culture) so that they can be translated and applied globally. They do not say, for example, that all individuals should have access to a high-tech AAC system (or eye tracking technology), as some individuals, in some situations, in some countries, may even struggle to access low-tech AAC systems or other basic resources. But they do say that an individual should have access to AAC (of unspecified form) at all times, as it is clear that all individuals with Rett syndrome require support from some form of AAC to maximise their communication potential. The guidelines have the potential to make a global impact and, for this, the content must be accessible. The creation of a ‘user-friendly’ handbook (ready for publication in spring 2019) is a start. There is further work to be done, follow-on projects to be developed with countries across the globe to translate the guidelines from English and to devise and monitor implementation programmes, working with local families and local therapists. In this respect the Rett Expertise Centre Netherlands-GKC is well-placed through its own collaborations with other Rett Expertise Centres and parent organisations, and through ERN ITHACA, to develop such projects.

Valorisation

This section reflects on the common threads that weave through the studies and discusses the societal impact of the applied research in the thesis. It includes implications for clinical practice, policy and decision-making, the potential impact on the lives of individuals with Rett syndrome and their families, and areas for further research. *“Delivering on Parental Wishes”* shows how the included studies respond to wishes expressed by parents of individuals with Rett syndrome, especially their desire for *“Earlier Diagnosis”* and *“Provision of Appropriate Treatments and Interventions Post-Diagnosis, Leading to Improved Quality of Life”*. This is followed by discussion of the *“Relevance”*, *“Target Groups”*, *“Activities and Products”*, *“Innovation”* and *“Schedule and Implementation”*.

Delivering on Parental Wishes

During the European Rett Syndrome conferences in Maastricht in 2013 and Berlin in 2017, ‘country updates’ sessions were arranged by the Rett Expertise Centre Netherlands-GKC and coordinated by the candidate for this PhD, in collaboration with Rett Syndrome Europe (RSE)⁷ and the organising team of each conference. During these sessions, representatives from Rett parent associations and foundations across Europe presented the situation within their country relating to Rett syndrome, for example, the organisations, experts and specialist services, resources and support structures available (or not available), and the aims that they were working towards. It was very clear that there were, and are, a number of ongoing and universal wishes dear to families of individuals with Rett syndrome irrespective of the country in which they live. These were described in **Chapter Three** and include the quest for an earlier and easier route to diagnosis, followed by provision of appropriate, timely, targeted treatments and interventions post-diagnosis which are not restricted by geography or finance. Naturally families desire a cure for Rett syndrome, something grounded in fundamental science (basic) research which is outside the scope of this thesis, but something that began to feel real and tangible with the first publication in 2007 of experiments showing phenotypic reversal in mouse models by Bird and colleagues [89], experiments that are continuing in various laboratories around the world to this day [90-99]. It is clear, however, that a cure is complex and still some way off [100, 101]. Therefore, parents also express more immediate concerns, concerns relating to the medical, paramedical, social and educational care and support required on a day by day basis. ‘Care today, cure tomorrow’ is a mantra by which many families live and many professionals operate. It underlies this thesis. Fundamental (basic) science research strives to find a way through genetic modification and/or a range of therapeutic (e.g. pharmacological) interventions to make the cure a reality and/or to alleviate the often severe medical symptoms associated with Rett syndrome, for example, breathing irregularities and epilepsy, with increasing numbers of clinical and drug trials coming on-stream at the present time. Applied research operates in tandem with basic research, and seeks to address the daily living needs of individuals and their families. In this thesis, a number of aspects relating to the daily communication challenges, the needs, and the potential of individuals with Rett syndrome have been explored; these will be re-framed below in order to show how they relate to the parental wishes for earlier diagnosis and for the provision of treatments and interventions that may lead to an improved quality of life for individuals with Rett syndrome and for their families.

⁷ Rett Syndrome Europe is an umbrella organisation, uniting Rett syndrome parent organisations across Europe.

Earlier Diagnosis

In order to diagnose individuals with Rett syndrome sooner, we need to know more about and understand the features of Rett syndrome better, at both a phenotypic as well as a genetic level. Advances in gene testing were described in **Chapter Two**. The value of advances in NGS, when applied to cases that would otherwise be difficult to detect (e.g. by conventional Sanger sequencing), was recently illustrated in relation to identifying mosaic *MECP2* variants in males showing clinical signs of Rett syndrome [102]. As NGS continues to develop and refine, as it becomes more affordable, it will become normal practice (rather than an exception) to carry out WES or even WGS whenever there is a query over a child's development. In the Netherlands, WES has been performed as standard since 2014, often covered by health insurance, whenever a genetic cause is suspected with a diagnosis of ASD, general intellectual impairment or neurological disorder [103].

What are the signs that might prompt an early request for genetic testing though? Studies such as that reported in **Chapter Six**, exploring markers of early social reciprocity, can make a contribution here. Retrospective video analysis can be a valuable tool for pinpointing phenotypic deviations from typical development and for comparing between syndromes and diseases as well as disease variants. According to Einspieler and Marschik "Succeeding to delineate the earliest RTT-specific atypicalities will lead to an earlier diagnosis and hence to earlier general symptomatic, but also targeted interventions. Furthermore, it would enable an earlier support and specific counselling of the families, who still find it to be a major cause of distress that professionals didn't listen to their concerns" [65 p. 329].

As features of Rett syndrome and its variants become increasingly uncovered, earlier diagnosis can also be aided through a universal commitment to sharing of the known genetic and phenotypic information in Rett specific or broader rare disease databases and registries. The study conducted in **Chapter Four** adds weight to this argument.

Provision of Appropriate Treatments and Interventions Post-Diagnosis, Leading to Improved Quality of Life

Provision of treatments and interventions appropriate to the needs of individuals with Rett syndrome relies on grounded information – a proper understanding of the disease, an analysis of the needs that have to be met, and an evaluation of responses to, and prior experiences of, different sorts of provision. It is on this foundation that the thesis is built rather than a collection of direct intervention studies.

An ability to communicate with others, with friends and family, relies on certain pre-requisites, and where any deficits in intact functioning are identified augmentation and appropriate supports are required to facilitate and maximise communication potential. **Chapter Five** offered a synthesis of recent knowledge in relation to development and on-going communication skills, and assessment and intervention approaches relevant to individuals with Rett syndrome. The research undertaken in **Chapters Seven and Eight**

explored one fundamental requirement underlying the use of eye gaze for communication. Given an intact oculomotor system, individuals with Rett syndrome have at least a solid starting point for using their eyes to communicate. Whether they then go on to communicate through unaided⁸ or aided⁹ means (low-tech or high-tech) or, preferably, a combination of these, is to some extent due to the preference of the individual, their family and the professionals working with them; the greatest influences on that decision are, however, more often related to constraints imposed by the human and physical environment – the levels of knowledge and support available, familiarity with techniques and systems, availability of equipment and funding, opportunities for communication. This was highlighted through the survey undertaken in **Chapter Nine**, which, although restricted to a Dutch sample, was in many ways representative of the experiences reported by families around the globe in the international guidelines project undertaken in **Chapter Ten**. The guidelines project also sought to address in a very practical way how evidence-based knowledge can be collated, analysed, and applied in order to build professional skills and understanding, something that should lead to provision of better communication support for individuals and families and ultimately lead to an enhanced quality of life.

Relevance

Rett syndrome is a rare disease, yet with 1 in 10-12,000 females [104-107], and fewer males [108-111], considered to have the disease, the number globally is not insubstantial. This thesis predominantly addresses issues related to the communications challenges, support needs and (hidden) potential of individuals with Rett syndrome. These are issues that go to the heart of an individual's interaction with the people close by and the wider world around. An ability to communicate, or being seen to have an ability to communicate, also impacts the attitudes and perceptions of the people and the world around an individual with Rett syndrome. Furthermore, this oftentimes influences the autonomy afforded an individual and the education open to them. As shown in **Chapter Five**, it is increasingly recognised that individuals with Rett syndrome have a greater cognitive and communicative potential than hitherto recognised. Use of eye gaze communication strategies is opening up the world for individuals who struggle with a body that presents many physical and health-related challenges. By paying attention to the eye gaze signals of individuals with Rett syndrome, and through the use of eye tracking technologies, researchers (and others) are beginning to develop a better understanding of the communication-related skills and abilities of individuals with Rett syndrome, beginning to recognise that communication potential is concealed beneath an outward surface of

⁸ Unaided communication = not using external tools to communicate but relying on the user's own body to convey messages. Examples include gestures, signs, or vocalizations.

⁹ Aided communication = using external tools, devices or systems to enhance communication. These may be electronic or non-electronic (high-tech or low-tech).

communication impairment. Studies such as the survey we conducted to evaluate (Dutch) families' experiences of eye gaze technology (**Chapter Nine**) and the project we led to develop international guidelines for management of communication through collection of survey data from large numbers of parents and professionals around the world, combined with extensive literature reviews (**Chapter Ten**), carry an impact at societal, policy-making, and service-planning levels. Both studies recognise the potentially heavy demands on time, resources and funding required to maximise communication potential, to develop appropriate ways to assess communication, to teach and implement appropriate intervention techniques and systems, and deploy appropriate management strategies. Funding for expensive eye tracking technology is not suggested as the only way forward in developing and promoting communication skills, but evidence from these studies (together with the evidence of intact oculomotor functioning) can be taken to health insurers and other funders in support of applications for devices. So, too, these studies can be used to argue for funding and time to allow for continuing professional development and for families and individuals to be offered sufficient, timely, ongoing support to enable them to fully implement communication strategies and systems. The value of multi-professional team collaboration is also recognised and is where Rett Expertise Centres can set an example of good working practice.

Target Groups

The research described in this thesis is of interest to anyone who works with and/or comes into contact with – i.e. anyone who communicates with – individuals with Rett syndrome and their families. That includes: doctors in specialised, hospital, and general practice settings; other healthcare workers in a range of settings; therapists (not just SLTs, but physio-, occupational- and music therapists etc.); assistive technology/AAC specialists; education staff and social services employees; caregivers, whether paid carers or family members; and, individuals with Rett syndrome themselves. It will also be of interest to legislation and policy makers, funders and service providers, for it contains recommendations relevant to multi-professional working, skills development, funding of equipment and resources, and, importantly, the fostering of parent-professional partnerships. The survey-based studies clearly demonstrate the benefits to be gained from building both professional and parental knowledge and skills, and from close professional-parent collaboration. These findings are illustrated by a recent conversation with a parent of a child with Rett syndrome, who said: *“I cannot even begin to tell you how important it is to have professionals in all disciplines who involve us and our child in discussions/consultations, who believe in them, who have in-depth knowledge of the condition. It gives us something to grab onto, some real visceral support. The emotional value is huge.”* If not managed well, however, there can be a tension in the professional-parent relationship, summed up by the same parent as: *“There is a massive discrepancy*

between what we as parents expect of therapists (and other professionals) in terms of knowledge and experience, and what they actually know/are able to provide in terms of support. I think by making both parties (and other professionals) aware of this alongside the panic, desperation and emotional vulnerability that parents are often feeling at the outset especially, some of the bad relationship/feeling that typically exists between the two parties might be alleviated." This thesis aims to contribute to the pool of shared knowledge, to create a common understanding between parents and professionals of some of the communication challenges, the communication support needs, and the communication potential of individuals with Rett syndrome.

Activities and Products

All of the research contained in this thesis has been shared with the national (Dutch) and international Rett syndrome communities through conference presentations in recent years. These have included both poster and oral presentations (as an invited speaker) in Chicago, Vienna, Berlin, Barcelona, Rome and St. Petersburg.

As a result of the country updates sessions held during the European Rett Syndrome conferences in Maastricht in 2013 and Berlin in 2017, an inventory of the situation regarding services and support for individuals with Rett syndrome and their families in countries across Europe was developed, showing both recent developments and current bottlenecks. This will continue to be updated at future European conferences.

An area of outstanding global interest has been the international project to develop guidelines for the management of communication, supported by funding from Rettsyndrome.org. One outcome of the project has been the development of an accessible ('user-friendly') handbook, primarily intended as a tool that parents can take and share with the professionals who work with their child (of any age), especially members of the communication team around their child and those who are responsible for resource planning and funding of communication services.

Closer to home one very practical outworking of the recommendations to build the skills of communication professionals has been the development of two national training and support networks for SLTs, jointly coordinated and led by the candidate for this PhD. The first was established in the Netherlands in March 2017, and the second, following the Dutch model, was formed in the UK in November 2018. Over the past two years the Dutch SLT network has grown to include more than 60 committed SLTs who participate in a regular programme of webinars, with two face-to-face study days per year. Both networks provide a creative platform for SLTs to come together and share elements of best practice, to present and discuss case studies, to provide and receive peer support and opportunities for mentorship, and to act as test grounds for implementation of the new international guidelines for communication. The networks are examples of cross-border collaboration and of professional-parent collaboration – the Dutch network being a collaboration

between the Rett Expertise Centre Netherlands-GKC, the NRSV and Stichting Terre, and the national speech and language therapy professional body (Nederlandse Vereniging voor Logopedie en Foniatrie, NVLF) while the UK network is a collaboration between Rett UK and the Royal College of Speech and Language Therapists (RCSLT). An active programme of parent support coffee mornings, AAC workshops and 'out and about' communication groups has also been established in both countries in the last two years as a direct consequence of the recommendations of research in this thesis. In addition, the networks model has begun to spread to other paramedical groups, with the creation in November 2018 of a national support and training network for Dutch physiotherapists working with individuals with Rett syndrome. With the Netherlands and UK acting as role models, it is anticipated that both the networks and the guidelines implementation strategies developed within the networks will be rolled out to other countries in the near future.

Innovation

The two national networks for SLTs working with individuals with Rett syndrome are new and innovative activities and offer testing grounds for further new and innovative approaches to implementing the new guidelines for communication.

In relation to the oculomotor research, a new protocol employing VR glasses as a new and innovative assessment tool has recently been developed in collaboration with the ENT Department at MUMC+. This is now ready for implementation during the next stage of the oculomotor research.

Schedule and Implementation

The oculomotor study will be extended in two ways. Firstly, the VR glasses will be coupled with the ENG testing, allowing for more personalised, motivational images and scenes to be introduced at a closer visual range. At a later stage, VT glasses may be trialled as an alternative method for registering eye movements, replacing the need for electrode attachment during testing. Both of these adaptations seek to combat the issues encountered during traditional ENG due to reduced motivation and attention, and poor signal quality. Secondly, cognitive and receptive language assessments will be added to the study, with support from eye tracking technology, to inform further elements of the complex matrix of pre-requisites to communication. This work will continue in collaboration with the ENT department of MUMC+.

Also at a national level, collaboration with the NRSV and Stichting Terre (and in the UK, with Rett UK) will continue, as the SLT networks continue to be supported and developed, and parent support is expanded. Web resources and online training materials (an e-learning platform) are planned as part of the roll out of professional-parent support. In the future, as the network model is extended to other countries there will be the potential to link the networks both across Europe and more globally, broadening opportunities for further

development of collaborative training and support for SLTs and other communication professionals specialising in Rett syndrome. These will be complementary to development of other paramedical networks (such as the Dutch physiotherapy network) and to involvement in ERN ITHACA, which is focused on a broader rare disease grouping.

Alongside the professional network development, collaborations will continue with European Rett parent organisations, including RSE as an umbrella organisation, and with Rett associations across the globe, for example, continuing the working relationship already established with Rettsyndrome.org. Also at the international level, leadership and collaboration on the communication guidelines will continue, with the accessible handbook published in spring 2019. This will be freely available as a download through all Rett syndrome associations and foundations in the 43 countries that participated in the project and any others who request it. Further resources, for example, guidelines webinars and streamlined versions of the guidelines targeted at specific professional groups (e.g. general practitioners) will be developed by the guidelines team once further funding is secured. Negotiations are also underway in a number of countries to develop follow-on projects to translate the guidelines and develop country-specific implementation and training plans.

Continuing international collaborations are also planned between the Rett Expertise Centre Netherlands-GKC and iDN @ Göttingen and Graz in order to extend the identification of early socio-communicative features of Rett syndrome through retrospective video analysis.

Conclusion

Of all the challenges faced by individuals, and their families, who are living with the complex rare disease that is Rett syndrome, communication difficulties have perhaps the greatest impact on quality of life as they go to the heart of establishing self-expression, autonomy and personhood. This thesis aimed to show that applied research undertaken within the context of a Rett Expertise Centre can make a positive contribution towards understanding and addressing the communication challenges, the communication support needs, and the (hidden) communication potential of individuals with Rett syndrome. Of special significance to all of these aspects are: the value of developing partnerships and networks; the need to increase (and disseminate) knowledge and understanding; and, the sharing of models and guidelines for good clinical practice. Expertise Centres have a central role as hubs for these core activities.

In the first instance, the importance of Expertise Centres in general, and of Rett Expertise Centres in particular, was highlighted. Within a (European) context of rare disease policies and national plans for delivery of services for rare diseases, Rett Expertise Centres like the Rett Expertise Centre Netherlands-GKC offer the potential to support individuals and families by recognising early signs and symptoms, by providing diagnostic and assessment services, and by contributing to genetic and phenotype, and longitudinal population-based

databases and registries. Expertise Centres can also provide second opinions and engage in intervention trials. Through collecting and analysing detailed genetic and phenotypic data, over time, we can gain greater understanding of rare diseases such as Rett syndrome, begin to understand more about the factors that interact with identified mutations to produce more or less severe phenotypes, and begin to understand more about treatments that can be prescribed for specific symptoms. By combining all of this with response to treatment data, we can also begin to predict how treatments might work and for whom they are most appropriate. This applies to paramedical, neurohabilitation-type interventions and therapies just as much as more genetic modification or pharmacological-based treatments and interventions.

Expertise Centres can offer support to fellow professionals by sharing skills and knowledge, both within and between countries, through formal rare disease networks like ERN ITHACA (of which the Rett Expertise Centre Netherlands-GKC is a member), or on a case-by-case basis in situations where expertise in a particular area is low and services are under-resourced. Networking between professionals, through the establishment of national support and training platforms like the SLT networks in the Netherlands and the UK, is invaluable. So too is stimulating partnerships with parent organisations, such as the NRSV and Stichting Terre, Rett UK, RSE, Rettsyndrome.org, and other national Rett syndrome associations and foundations. Such networks and partnerships provide ready outlets for the sharing of knowledge, information, skills, and resources, in short, for the sharing of models of good clinical practice and for the sharing of clinical practice guidelines.

All of this must be built on research, research that helps us understand more about specific elements underlying a disease like Rett syndrome, more about the origins and development of the disease as well as its ongoing course and consequences, research that helps us test and evaluate assessment models and interventions so that we can construct new perspectives, set new expectations and devise new opportunities for the individuals in questions. In this thesis, research was presented on one of the early developmental markers, response to name, as a contribution towards the delineation of early socio-communicative profiles of Rett syndrome and its variants. Research was presented relating to one element in the complex matrix of pre-requisites underlying the use of eye gaze for communication, that of oculomotor function, and offered as a starting point upon which to build core skills. Research was presented that described families' experiences of using eye tracking technology to build and maximise their child's functional communication skills, and their need for greater support was highlighted. New perspectives were also offered on the communicative and cognitive competencies of individuals with Rett syndrome in order to underline the need to set new expectations and to open up new communication opportunities. Ultimately, all of these aspects were brought together in the creation of the clinical guidelines for the assessment, intervention and long-term management of communication in individuals with Rett syndrome. This piece of international research – based on available evidence, lived experience and expert consensus – has the potential for

global impact. The guidelines are grounded firmly in recognition of the communication needs of individuals and their families, in the context of the everyday communication challenges they face, while believing in the communication potential of individuals with Rett syndrome, and desiring to improve quality of life through provision of better support for individuals, their families and the professionals who work with them.

Elevating our understanding of the outward and underlying features of Rett syndrome, enhancing professional and parental knowledge and skills, and empowering professional-parent partnerships are all key to improving the current communication opportunities – the ‘care for today’ – afforded to individuals with Rett syndrome, while simultaneously seeking a ‘cure for tomorrow’.

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Appendix

Clinical Guidelines for the Assessment, Intervention and Long Term Management of
Communication in Individuals with Rett Syndrome

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Appendix 1

Guiding Principles

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%) ⁱ
Rights & Beliefs	Rights Of The Individual With Rett Syndrome		
	In accordance with the UN Convention on the Rights of Persons with Disabilities, all individuals with Rett syndrome have the following rights with regard to communication:		
1	Right to be treated with respect.	Strongly agree	36/36 (100%)
2	Right to comprehensive multidisciplinary assessment of their strengths and needs.	Strongly agree	34/36 (94.4%)
3	Right to an appropriate communication system.	Strongly agree	36/36 (100%)
4	Right to appropriate communication goals.	Strongly agree	35/36 (97.2%)
5	Right to timely review and modification of goals in line with changing needs.	Strongly agree	35/36 (97.2%)
6	Right to advice, support and services which start early and continue throughout life.	Strongly agree	35/36 (97.2%)
7	Right to advice and support from knowledgeable and expert communication professionals.	Strongly agree	35/36 (97.2%)
8	Right to communication partners who are trained in appropriate communication strategies and techniques.	Strongly agree	34/36 (94.4%)
9	Right to be offered activities appropriate to their age interests and culture.	Strongly agree	34/36 (94.4%)
10	Right to make choices.	Strongly agree	36/36 (100%)
11	Right to participate in society.	Strongly agree	36/36 (100%)

12	Right to education.		Strongly agree	35/36 (97.2%)
13	The Communication Bill of Rights is a valuable resource for promoting communication as a basic right.		Strongly agree	34/36 (94.4%)
	Beliefs And Attitudes			
14	All communication partners should believe that the individual with Rett syndrome is capable of communicating.		Strongly agree	36/36 (100%)
15	The potential to communicate is frequently underestimated in individuals with Rett syndrome.		Strongly agree	34/36 (94.4%)
16	For any individual with Rett syndrome, their level of receptive language (understanding) is usually better than their ability to express themselves.		Strongly agree	35/36 (97.2%)
17	Communication partners should believe that, given the opportunity, individuals with Rett syndrome will be able to communicate using AAC.		Strongly agree	32/35 (91.4%)
18	Communication partners should have an open mind to the communication potential of the individual with Rett syndrome.		Extremely important	36/36 (100%)
19	Communication partners should spend time getting to know the individual with Rett syndrome in order to build a relationship.		Extremely important	34/36 (94.4%)
20	Communication partners should be patient and persistent.		Extremely important	35/35 (100%)

¹n/N (%) = participants with median response or one category either side

Professional Practice

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%) ⁱ
Professional Practice	Principles Of Teamwork		
1	Every individual with Rett syndrome should be supported by a multidisciplinary team.	Strongly agree	34/36 (94.4%)
2	The team should share a common vision and work collaboratively to define and agree communication goals and support plans.	Strongly agree	35/36 (97.2%)
3	The team should incorporate all significant communication partners and may include the individual with Rett syndrome, their parents/other family members, AAC specialists, SLP, OT, PT, Rett specialist staff, and other key people in the individual's life.	Strongly agree	34/36 (94.4%)
4	At a minimum the team will consist of the SLP, parents or other family members/caregivers and the individual with Rett syndrome.	Strongly agree	31/36 (86.1%)
5	Team members should discuss expectations and define each other's roles, for example, who will be responsible for programming devices or modifying page sets. This should occur at the start of their work and whenever a team member changes.	Strongly agree	33/35 (94.3%)
6	One person in the team should be identified as the "key person" with responsibility for monitoring communication goals. Monitoring refers to making sure the therapy plan is being carried out as agreed and alerting the rest of the team when changes are needed.	Strongly agree	34/35 (97.1%)
7	The "key person" should be someone who is knowledgeable about Rett syndrome and works with the individual with Rett syndrome regularly. This may be a teacher, teaching assistant, family member or other person in the team.	Strongly agree	34/35 (97.1%)
8	It is the role of the communication professional to train other communication partners in communication techniques and strategies that will benefit the individual with Rett syndrome.	Strongly agree	34/35 (97.1%)

9	It is the role of the communication professional to reinforce training by providing easy to read handouts and instructions.	Agree	32/36 (88.9%)
10	It is the role of the communication professional to work with the family and other communication partners to choose the appropriate page sets and/or vocabulary to build into any AAC system or device.	Strongly agree	33/36 (91.7%)
	Responsibilities Of Professionals		
11	Professionals should engage in reflective practice, with the aim of building their own confidence and knowledge about the area.	Strongly agree	33/36 (91.7%)
12	Professionals should keep their knowledge and understanding of Rett syndrome up to date so that they are aware of recent trends in the literature and in clinical practice.	Strongly agree	36/36 (100%)
13	Professionals should keep their knowledge and understanding of AAC up to date so that they are aware of recent trends in the literature and in clinical practice.	Strongly agree	34/35 (97.1%)
14	Professionals should use an evidence-based practice model to guide their clinical decision-making, incorporating information from the literature, clinical experience, and the wishes of the individual with Rett syndrome and their family.	Strongly agree	34/35 (97.1%)
15	Professionals who are inexperienced in working with individuals with Rett syndrome should seek training in relevant topics.	Strongly agree	36/36 (100%)
16	Organizations employing new or inexperienced professionals to work with individuals with Rett syndrome have a duty to enable those professionals to receive training in relevant topics.	Strongly agree	35/35 (100%)
17	Professionals who are inexperienced in working with Rett syndrome should seek advice and support from colleagues with more specialist knowledge and expertise in the area.	Strongly agree	36/36 (100%)
18	Professionals who are working in isolation (e.g. working as an independent practitioner) should connect with the other members of the broader team who are working with the individual and family so that support and advice and recommendations are coordinated.	Strongly agree	36/36 (100%)

19	Professionals should engage with the broader Rett syndrome community and be able to direct caregivers/communication partners to relevant information and support networks in that community. e.g. through social networks, conferences, websites, online courses, etc.	Strongly agree	35/36 (97.2%)
20	Professionals should work with caregivers/communication partners to problem solve.	Strongly agree	36/36 (100%)
Rett Specialist Clinics And Expertise Centers			
21	The individual and family may be referred to a Rett Specialist Clinic or Expertise Center in order to get a diagnosis, or for specialized assessment and advice or a second-opinion at any point following diagnosis.	Strongly agree	34/35 (97.1%)
22	Visits to a Rett Specialist Clinic or Expertise Center may be as a one-off or at regular (e.g. annual) intervals.	Strongly agree	31/35 (88.6%)
23	It is unlikely that the Rett Specialist Clinic or Expertise Center will deliver ongoing, day to day therapy and intervention.	Agree	33/34 (97.1%)
24	Referral to a Rett Specialist Clinic or Expertise Center will be dependent on location as these services are not available everywhere.	Strongly agree	26/35 (74.3%)
25	Communication professionals attached to the Rett Specialist Clinic or Expertise Center should always make contact with the locally-treating communication professional(s) to discuss the individual's communication, to share the results of any assessments, and to discuss goals for intervention.	Strongly agree	32/35 (91.4%)
26	Communication professionals attached to a Rett Specialist Clinic or Expertise Center should be available to offer advice and support to, and answer questions from, locally-treating therapists.	Strongly agree	34/34 (100%)
27	Communication professionals attached to a Rett Specialist Clinic or Expertise Center should provide training and instruction, and access to resources, for locally-treating therapists.	Strongly agree	32/35 (91.4%)

28	Communication professionals attached to a Rett Specialist Clinic or Expertise Center should be available to respond to questions from parents and caregivers and individuals with Rett syndrome.	Strongly agree	35/35 (100%)
29	Rett Specialist Clinics or Expertise Centers may provide consultations and support through video conferencing for individuals who are unable to visit a clinic or center in person.	Strongly agree	35/35 (100%)

Features of Rett Syndrome and Co-Existing Conditions that Impact Communication

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%)ⁱ
Rett Features			
1	Communication skills of individuals with Rett syndrome will fluctuate based on internal and external factors. Expect inconsistency.	Strongly agree	33/36 (91.7%)
	The Following Features Of Rett Syndrome Are Likely To Impact Communication:		
2	- Hand stereotypies.	Strongly agree	29/35 (82.9%)
3	- Breathing/respiratory difficulties.	Agree	30/34 (88.2%)
4	- Impaired sleep pattern.	Agree	31/34 (91.2%)
5	- Scoliosis/kyphosis.	Agree	32/34 (94.1%)
	The Following Conditions Which May Co-Exist Alongside Rett Syndrome Are Likely To Impact Communication:		
6	- Epileptic seizures.	Strongly agree	33/33 (100%)
7	- Vacant spells.	Strongly agree	32/33 (97%)

8	- Fatigue/reduced alertness.	Strongly agree	33/35 (94.3%)
9	- Heightened anxiety.	Strongly agree	31/35 (94.3%)
10	- Dyspraxia/apraxia.	Strongly agree	33/34 (97.1%)
11	- Dystonia.	Agree	32/34 (94.1%)
12	- Difficulties with sensory regulation (over- or under-stimulation).	Agree	34/35 (97.1%)
13	- Hearing loss.	Agree	29/35 (82.9%)
14	- Auditory processing difficulties.	Agree	28/34 (82.4%)
15	- Impaired visual acuity.	Agree	31/33 (93.9%)
16	- Impaired visual field.	Agree	29/33 (87.9%)
17	- Oculomotor apraxia.	Agree	30/32 (93.8%)
18	- Cortical visual impairment.	Agree	32/34 (94.1%)
19	- Gastrointestinal issues.	Agree	33/34 (97.1%)

Strategies to Optimize Engagement with Individuals with Rett Syndrome

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%) ⁱ
Strategies	When communicating with individuals with Rett syndrome in any situation, it is extremely important that communication partners:		
1	- make eye contact with the individual with Rett syndrome.	Extremely important	34/36 (94.4%)

2	- address and talk directly to the individual with Rett syndrome rather than talking about them in their presence.	Extremely important	34/35 (97.1%)
3	- are consistent (in approach, language and vocabulary used).	Extremely important	35/36 (97.2%)
4	- are engaging and fun.	Extremely important	33/36 (91.7%)
5	- are responsive, acknowledging and reinforcing all communication attempts.	Extremely important	34/36 (94.4%)
6	- give feedback and attribute meaning (saying aloud what you think the individual's response/action/behavior means).	Extremely important	35/36 (97.2%)
7	- explain what is happening now and what is going to happen next.	Extremely important	34/36 (94.4%)
8	- use multimodal communication (facial expression, gestures, vocalizations, speech alongside AAC) whenever talking to an individual with Rett syndrome.	Extremely important	33/36 (91.7%)
9	- make the individual's AAC system(s) or device(s) available at all times.	Extremely important	33/36 (91.7%)
10	- adapt natural situations and activities so that opportunities for communication are created.	Extremely important	35/36 (97.2%)
11	- follow the individual's lead.	Extremely important	34/36 (94.4%)
12	- make sure vocabulary, topics and activities are appropriate to the interests of the individual with Rett syndrome.	Extremely important	31/35 (88.6%)
13	It is extremely important to provide access to a range of activities.	Extremely important	33/36 (91.7%)
14	It is also very important to incorporate music into activities.	Very important	33/36 (91.7%)
	When communicating with individuals with Rett syndrome in any situation, it is very important that communication partners:		
15	- attract and maintain the individual's attention by varying tone and intensity of voice.	Very important	26/35 (74.3%)

16	- attract and maintain the individual's attention by using varied body movements, facial expression and gestures.	Very important	26/35 (74.3%)
17	- keep communication in the 'here and now.'	Very important	32/36 (88.9%)
	When communicating with individuals with Rett syndrome in any situation, communication partners should:		
18	- decrease motor demands as the cognitive load of a task increases.	Strongly agree	28/33 (84.8%)
19	- pay attention to behaviors that indicate the need for a change in position or a change/break in activity.	Strongly agree	35/35 (100%)
20	When in a more structured setting. i.e. in an assessment or intervention (therapy or teaching) session, it is very important to reduce distractions.	Very important	36/36 (100%)
21	Individuals with Rett syndrome may have a delayed response in communication interactions.	Strongly agree	34/35 (97.1%)
22	Response delay may be for a few seconds up to a minute or more.	Strongly agree	31/35 (88.6%)
	To determine sufficient wait time for a particular individual with Rett syndrome, communication partners can:		
23	a. Observe the individual with Rett syndrome to identify typical communication behavior.	Strongly agree	35/35 (100%)
24	b. Review videos of communication interactions to identify typical communication behavior.	Strongly agree	35/35 (100%)
25	c. Discuss typical communication behavior with familiar communication partners.	Strongly agree	35/35 (100%)
26	d. Consider how the features of Rett syndrome and any co-existing conditions may impact response time.	Strongly agree	33/35 (94.3%)

Assessment

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%)ⁱ
Assessment – Principles	General Principles Of Assessment		
1	Assessment should be informed (based on an understanding of Rett syndrome in general and the needs of the individual in particular), comprehensive and holistic.	Strongly agree	31/34 (91.2%)
2	Initial assessment should include a detailed history of medical and physical status, including: any visual and hearing problems, breathing and respiratory difficulties, seizures, fine and gross motor control (including ambulation, head control, postural control, hand function, scoliosis).	Strongly agree	32/35 (91.4%)
3	Subsequent assessments should always capture information on current medical and physical status.	Strongly agree	31/35 (88.6%)
4	Assessment should consider the skills and needs of the individual with Rett syndrome as well as the skills and needs of the communication partners.	Strongly agree	31/33 (93.9%)
5	Assessment should consider the opportunities and barriers to communication that may be present in various environments (e.g. home, school, social settings).	Strongly agree	33/34 (97.1%)
6	Dynamic assessment is “an interactive, test-intervene-retest model of psychological and psychoeducational assessment” (Haywood & Lidz, 2007). Given the definition above: Assessment should not take place at a single moment in time, it should be ongoing and dynamic.	Strongly agree	33/34 (97.1%)
7	Dynamic assessment means that there will often be an overlap between assessment and intervention.	Strongly agree	30/31 (96.8%)

8	Standardized assessments may not accurately reflect an individual's underlying ability nor their communicative and learning potentials but they may be adapted to obtain information on certain specific skills.	Strongly agree	33/34 (97.1%)
9	Standardized assessments of language and cognition are likely to indicate that individuals with Rett syndrome have an intellectual disability.	Agree	27/31 (87.1%)
10	Adaptions to standardized assessments can include modifying presentation of test materials such as mounting test items on a board and use of partner assisted scanning, eye gaze, or other AAC strategies as response modalities.	Strongly agree	31/33 (93.9%)
11	Adapted standardized assessments can be used to assess expressive language, receptive vocabulary and cognition.	Agree	29/31 (93.5%)
12	The World Health Organization's International Classification of Functioning, Disability and Health (ICF) is an appropriate model around which to structure holistic assessment of the individual.	Agree	21/22 (95.5%)
Assessment – People & Context	People Involved In Assessment		
1	Due to the complexity of their communication needs, assessment of individuals with Rett syndrome should be part of a team process.	Strongly agree	34/35 (97.1%)
2	The outcome of the assessment should not rely on the judgement of one professional in isolation.	Strongly agree	33/35 (94.3%)
3	Assessment of communication needs and skills should include contributions from all significant communication partners. This means: parents and other family members, caregivers, teacher(s), therapists (e.g. SLP, OT, PT, Music), peers.	Strongly agree	36/36 (100%)
4	A wider group of professionals may be involved in the assessment of specific areas such as hearing, vision and motor control. This could include an audiologist, ophthalmologist, physical therapist, occupational therapist, neurologist or others.	Strongly agree	33/34 (97.1%)

	Assessment Of The Individual		
	Assessment of the individual should gather information on a broad range of communication-related aspects:		
5	- The individual's nonverbal skills (e.g. referential gaze, eye pointing, joint attention).	Strongly agree	35/35 (100%)
6	- The individual's level of cognitive awareness (e.g. understanding of cause and effect, vocabulary, reasoning).	Strongly agree	30/35 (85.7%)
7	- How the individual communicates currently.	Strongly agree	34/35 (97.1%)
8	- The range of communicative functions used by the individual with Rett syndrome.	Strongly agree	35/35 (100%)
9	- The strategies/systems that have been tried in the past.	Strongly agree	32/35 (91.4%)
10	- The strategies/systems that have been successful and unsuccessful.	Strongly agree	33/35 (94.3%)
11	- The types of activities and topics that the individual with Rett syndrome is interested in and motivated by.	Strongly agree	34/35 (97.1%)
12	- The status of the individual's oral-motor skills.	Agree	28/34 (82.4%)
13	Assessment should include identification of the most appropriate access method for an individual (e.g. eyes, hands).	Strongly agree	34/35 (97.1%)
	Assessment Of The Broader Context		
	Assessment of the broader context around an individual should include:		
14	- Identification of social networks (Blackstone, 2012) and communication partners.	Strongly agree	27/29 (93.1%)
15	- Identification of the knowledge and skills and training needs of communication partners.	Strongly agree	29/32 (90.6%)

16	- Identification of opportunities for communication and barriers to communication within the social environment.	Strongly agree	35/35 (100%)
Assessment – Procedures & Settings	Assessment Procedures		
1	A variety of assessment procedures should be used to provide a comprehensive assessment of the communicative, cognitive and interactive skills of an individual with Rett syndrome.	Strongly agree	34/34 (100%)
	Assessment can be conducted through any combination of the following:		
2	- Interviews with significant communication partners.	Strongly agree	32/32 (100%)
3	- Questionnaires completed by significant communication partners.	Strongly agree	30/32 (93.8%)
4	- Observations of the individual in natural settings.	Strongly agree	33/33 (100%)
5	- Informal assessments in modified natural settings or structured sessions.	Strongly agree	31/32 (96.9%)
6	- Modified formal (standardized) assessments	Agree	25/31 (80.6%)
7	- Videotaping of the individual in natural settings.	Strongly agree	30/33 (90.9%)
8	- Videotaping of the individual in structured sessions.	Strongly agree	27/33 (81.8%)
	Assessment Settings		
9	Assessments should be undertaken in natural or naturalistic settings.	Strongly agree	28/31 (90.3%)
10	Observations should be conducted in a range of communication environments and with a range of communication partners.	Strongly agree	30/31 (93.5%)

	Other Considerations For Assessment		
11	Informal assessment includes the use of objects, photographs, picture symbols, and written letters and words.	Agree	34/34 (100%)
12	Music can be a valuable medium for observing the behavior of an individual with Rett syndrome and can be a valuable component of assessment.	Agree	31/33 (93.9%)
13	Eye gaze is the best access method for assessment of cognition.	Agree	26/33 (78.8%)
14	Eye gaze is the best access method for assessment of receptive and expressive language skills.	Agree	26/33 (78.8%)

AAC Assessment

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%)ⁱ
AAC Assessment	Starting Point – Assessment Of Readiness For AAC		
1	There are no prerequisite skills that must be demonstrated before aided AAC should be considered.	Strongly agree	27/31 (87.1%)
2	At the time of diagnosis individuals with Rett syndrome should be referred for AAC evaluation.	Strongly agree	26/35 (74.3%)
	AAC Assessment – Models Of Best Practice		
3	The six-step process (Dietz et al., 2012) is an appropriate model to use for the assessment of individuals with Rett syndrome.	Agree	14/17 (82.4%)
4	The Participation Model (Beukelman & Mirenda, 2013) is a model for best practice in AAC assessment that should be utilized for individuals with Rett syndrome.	Strongly agree	14/15 (93.3%)

5	Feature Matching (Beukelman & Mirenda, 2013) is a model for best practice in AAC assessment that should be utilized for individuals with Rett syndrome.	Agree	11/12 (91.7%)
6	The model of communicative competence (Light & McNaughton, 2014) can guide AAC assessment and intervention.	Strongly agree	21/21 (100%)
	Components Of AAC Assessment		
	AAC assessment should include consideration of a broad range of aspects:		
7	- Multiple modalities e.g. unaided (facial expression, gestures, vocalizations) and aided communication (low and high tech).	Strongly agree	31/31 (100%)
8	- Both high and low tech AAC (depending on availability).	Strongly agree	31/32 (96.9%)
9	- A range of symbol systems.	Agree	25/31 (80.6%)
10	- Layout (e.g. size and number of options/pictures on the communication board or screen).	Strongly agree	31/32 (96.9%)
11	- Complexity of vocabulary on offer.	Strongly agree	28/31 (90.3%)
12	- Options for alternative access (e.g. eye gaze, touchscreen, switch control).	Strongly agree	30/32 (93.8%)
13	- Positioning (of individual and device, AAC system).	Strongly agree	31/32 (96.9%)
	Assessment Of Readiness For Eye Gaze Technology		
14	Overall health, motor skills, visual attention and memory, motivation, ability to focus on the screen and prior experience with aided AAC will impact ability to access eye gaze technology. A comprehensive assessment of these features can determine whether an individual is a strong candidate for eye gaze or if the individual will benefit from additional investigation or trial of an alternate access method.	Agree	26/34 (76.5%)
15	Assessments of readiness to use eye gaze technology are best conducted through informal activities.	Agree	29/30 (96.7%)

16	Assessment activities should be personalized as far as possible. e.g. introducing photographs of familiar people into on-screen activities.	Agree	28/30 (93.3%)
17	The same activities used to assess readiness can also be used to train/build the skills that are necessary for use of eye gaze technology for communication.	Strongly agree	26/30 (86.7%)
18	If an individual does not seem to be interested or motivated to engage with eye gaze technology during the assessment it should not be discounted as a possible access method.	Agree	29/30 (96.7%)
19	An individual does not have to 'pass' assessment at an early level of screen use (e.g. demonstrating cause-effect understanding) before their response to more advanced levels of eye gaze technology use can be assessed (e.g. introducing them to grids for communication).	Agree	25/29 (86.2%)
20	It is not necessary to achieve successful calibration on an eye gaze device in order to assess eye gaze as an access method.	Agree	21/28 (75%)
21	Interactive games can be used to establish calibration of eye gaze over time.	Agree	28/28 (100%)
22	It is important to make video-recordings of an individual's responses during assessments for eye gaze technology.	Agree	29/30 (96.7%)
23	It is valuable to record/track an individual's on-screen gaze pattern and eye movements during assessments for eye gaze technology.	Agree	31/31 (100%)

Assessment of AAC System/Device

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%) ⁱ
Trial Periods	Trial Periods As Assessment For An AAC System Or Device		
1	Trial periods are essential for assessing whether any AAC system or device is appropriate for an individual.	Strongly agree	34/36 (94.4%)
2	Trial periods are essential for assessing suitability of both low and high tech systems or devices.	Strongly agree	29/35 (82.9%)
3	Suitability of an AAC system or device cannot be judged adequately from a single session or a single point in time.	Strongly agree	36/36 (100%)
4	Trial periods should be for a minimum of 8 weeks to ensure the individual with Rett syndrome gets a real chance to learn about and (attempt) to use the device/system.	Strongly agree	29/34 (85.3%)
5	Trial periods should be for a minimum of 8 weeks to ensure the individual's primary/key communication partners get a real chance to learn about and to use the device/system.	Strongly agree	29/34 (85.3%)
6	Trial periods should be free/at no cost to the end user at point of use.	Strongly agree	32/36 (88.9%)
7	Individuals should be allowed more than one trial of the same AAC system or device (e.g. if the first trial was judged unsuccessful due to poor health at that point in time).	Strongly agree	33/36 (91.7%)
8	Individuals should be able to trial more than one or multiple AAC systems and devices.	Strongly agree	34/36 (94.4%)
9	During trial periods the system/device should be used in multiple environments and with multiple communication partners.	Agree	29/32 (90.6%)
10	During trial periods the individual with Rett syndrome and their primary/key communication partners should be well-supported by knowledgeable and experienced professionals who are familiar with/trained to use the system/device on trial.	Strongly agree	36/36 (100%)

11	The professionals who offer support during a trial may include advisors who work for the communication aid company supplying the device and/or an SLP, OT, AAC/Assistive technology specialist advisor and/or others who are experienced with the device/system on trial.	Strongly agree	32/35 (91.4%)
Device Features	Assessment Of Device-Specific Features		
	When assessing the suitability of a device for an individual, it is extremely important to take the following features into consideration:		
1	- Portability	Extremely important	31/36 (86.1%)
2	- Options for mounting on a wheelchair, table, wall.	Extremely important	33/36 (91.7%)
3	- Robustness (durability).	Extremely important	33/36 (91.7%)
4	- Ability to adjust response time/sensitivity of responses.	Extremely important	33/36 (91.7%)
5	- Availability of funding/approval for funding.	Extremely important	31/35 (88.6%)
6	- Support from a wider community of families using the same device/software (including online communities) e.g. for sharing of page sets, help with troubleshooting.	Extremely important	28/35 (80%)
7	- Ease of repair in case of problems/breakdown.	Extremely important	31/35 (88.6%)
	When assessing the suitability of a device for an individual, it is very important to take the following features into consideration:		
8	- Size.	Very important	35/36 (97.2%)
9	- Weight.	Very important	30/36 (83.3%)
10	- Battery life	Very important	32/36 (88.9%)

11	- Use in different environments e.g. outside in sunshine and rain.	Very important	34/36 (94.4%)
12	- Range of software available (including language programs and symbol sets and any the individual is already familiar with).	Very important	35/35 (100%)
13	- Availability of pre-made page sets in the relevant language.	Very important	31/34 (91.2%)
14	- Complexity of programming required to personalize/adapt the device to suit the end user.	Very important	34/35 (97.1%)
15	- Level of technical skill/knowledge required by communication partners.	Very important	35/35 (100%)
16	- Support and training offered by supplier during a trial period.	Very important	34/35 (97.1%)
17	- Long-term technical support and after-care offered by the supplier.	Very important	34/34 (100%)
18	- Obsolescence (age of model and remaining length of time that support, updates to software, parts etc. will be available).	Very important	33/35 (94.3%)
19	- Capacity/functions available within the device.	Very important	34/35 (97.1%)
20	- Cost to purchase.	Very important	34/35 (97.1%)
21	- Cost of insurance.	Very important	33/35 (94.3%)
22	The potential for the individual to access the internet, social media and control their environment should also be considered.	Agree	25/32 (78.1%)

Intervention

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%)ⁱ
Intervention – Principles	General Principles Of Intervention		
1	Advice and information about the potential for communication should be provided at diagnosis or shortly thereafter.	Strongly agree	32/35 (91.4%)
2	Communication intervention and management should start early and be lifelong.	Strongly agree	35/35 (100%)
3	Communication intervention will help to develop functional communication skills, promote cognitive development, provide a foundation for literacy development, and improve social communication.	Strongly agree	34/35 (97.1%)
4	Communication intervention will help the individual with Rett syndrome to become more autonomous as a communicator. Autonomous refers to an individual being able to communicate what they want to say, to whoever they want to say it, whenever and wherever they want to say it using any form of communication.	Strongly agree	33/34 (97.1%)
5	Communication intervention and management should be reviewed regularly to make sure that it is always appropriate to the needs of the individual.	Strongly agree	35/35 (100%)
6	It is preferable that intervention takes place in a naturalistic context.	Strongly agree	30/34 (88.2%)
7	Individuals should be given frequent opportunities for practice.	Strongly agree	35/35 (100%)
Intervention – Developing Goals	Developing Goals For Intervention		
8	Goals for intervention should include development of nonverbal, low-tech and high-tech strategies.	Strongly agree	31/35 (88.6%)

9	Goals should be planned to follow the typical stages of child development.	Agree	28/34 (82.4%)
10	Goals for intervention should aim to increase the frequency, variety, complexity and clarity of communication so that individuals can interact with a wide range of communication partners.	Strongly agree	31/33 (93.9%)
11	Goals should be developed that consider the needs and preferences of the individual, their caregivers and other important communication partners.	Strongly agree	33/33 (100%)
12	The SMART (Specific, Measurable, Agreed upon, Realistic, Time-based) framework can be used to develop communication goals.	Strongly agree	22/23 (95.7%)
Intervention – Techniques			
1	Expanding is a technique used to re-word and increase the complexity of a word or a phrase to make it more complete. Expanding can be used in communication intervention for individuals with Rett syndrome.	Strongly agree	24/27 (88.9%)
2	Aided language stimulation is a strategy where the communication partner combines verbal output with aided AAC in order to support receptive language and to provide vocabulary. The partner may select vocabulary on the individual's own AAC system or use another AAC system as they talk. Aided language stimulation can be used in communication intervention for individuals with Rett syndrome. Aided language stimulation may also be known as Aided language modelling or Augmented language input.	Strongly agree	28/29 (96.6%)
3	Modeling is a strategy where the communication partner uses the individual's own AAC system when talking with them in order to teach by example. Modelling can be used in communication intervention for individuals with Rett syndrome.	Strongly agree	29/31 (93.5%)
4	Video modeling is a visual teaching method that involves watching a video of someone modeling a targeted behavior or skill and then imitating the desired behavior or skills. Video modeling can be used in communication intervention for individuals with Rett syndrome.	Agree	24/29 (82.8%)
5	Recasting is a technique used to correct errors so that communication is not obstructed. When an error is produced, the communication partner will repeat the error back to the learner in a corrected form. Recasting can be used in communication intervention for individuals with Rett syndrome.	Agree	21/27 (77.8%)

6	Prompts or cues such as gestures, demonstrations, touch, and signals can be used to increase the likelihood that individuals will make correct responses.	Agree	27/31 (87.1%)
7	Errorless learning involves providing prompts or cues immediately following a stimulus to ensure the individual provides a correct response. Errorless learning can be used in communication intervention for individuals with Rett syndrome	Agree	22/29 (75.9%)

Targets and Goals for Intervention

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%)ⁱ
Goals – Functions	Communication Functions		
1	Goals to expand the range of communicative functions (e.g. requests, answers, protests, comments, questions, descriptions, greetings) should be included in intervention programs for individuals with Rett syndrome.	Strongly agree	29/31 (93.5%)
2	Developing a yes/no response is important for all individuals with Rett syndrome.	Strongly agree	32/35 (91.4%)
3	Yes/no responses can be used to express agreement or disagreement, make choices and/or answer questions.	Strongly agree	34/35 (91.7%)
4	To expand an initial vocabulary, goals should include words that cover a range of ideas, interests and meanings including emotions, social and academic language.	Strongly agree	29/32 (90.6%)
5	Language intervention should begin with exposure to a robust vocabulary (including core and fringe words) so that potential for communication is unlimited.	Strongly agree	26/32 (81.3%)
6	Limiting the options or choices given is appropriate for some individuals with Rett syndrome when there is a risk for frustration, access issues or a robust language system has been trialed for at least 12 months with limited success.	Agree	25/31 (80.6%)
7	An individual's vocabulary will change according to age, communication partner, language development, environment, mood, and context. The vocabulary used in an AAC system should allow for the same change and flexibility.	Strongly agree	31/32 (96.9%)

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Goals – Ways	Ways Of Communicating		
1	Communication should be developed across multiple modalities informed by the comprehensive and holistic assessment of the individual and their communication partners.	Strongly agree	33/34 (97.1%)
	Facial expressions		
2	Facial expressions such as smiling and frowning should be acknowledged as potentially communicative in individuals with Rett syndrome.	Strongly agree	33/35 (94.3%)
	Body movements		
3	Body movements such as leaning and/or moving towards or away from objects or people should be acknowledged as potentially communicative in individuals with Rett syndrome.	Strongly agree	34/34 (100%)
4	Goals for maintaining body movements are appropriate for individuals who already use body movements such as walking towards items for communicative purposes.	Strongly agree	33/35 (94.3%)
	Gestures		
5	Gestures such as reaching, pointing and/or waving should be acknowledged as potentially communicative in individuals with Rett syndrome.	Strongly agree	32/35 (91.4%)
6	Goals for developing or maintaining gestures such as reaching, pointing and/or waving are appropriate for individuals who already demonstrate some voluntary hand control.	Agree	31/35 (88.6%)
7	Strategies can be developed to reduce hand stereotypies if they are judged to interfere with communication.	Agree	33/34 (97.1%)
8	Strategies to reduce hand stereotypies must be tailored to the individual, be well-tolerated, and acceptable to the individual and their significant others. These strategies can include splinting, holding or positioning the arm, and/or use of highly motivating activities.	Strongly agree	33/34 (97.1%)

	Oral speech skills		
9	Vocalizations should be acknowledged as potentially communicative in individuals with Rett syndrome.	Strongly agree	32/34 (94.1%)
10	Goals for developing or maintaining sound production are appropriate for individuals who already produce sounds voluntarily.	Agree	27/31 (87.1%)
11	Spoken words or sentences should be acknowledged as communicative in individuals with Rett syndrome, even if echolalic or highly repetitive in nature.	Agree	32/34 (94.1%)
12	Goals for developing or maintaining spoken words or sentences are appropriate for individuals who already produce spoken words or word approximations.	Agree	29/31 (93.5%)
13	Intervention for developing or maintaining sound production, spoken words or sentences should be combined with aided AAC.	Strongly agree	26/31 (83.9%)
	Eye gaze		
14	Looking at objects, individuals and/or pictures should be acknowledged as potentially communicative in individuals with Rett syndrome.	Strongly agree	34/35 (97.1%)
15	Goals for developing or maintaining eye gaze such as looking at objects, individuals and/or pictures are appropriate for individuals with Rett syndrome.	Strongly agree	33/35 (94.3%)
	Symbols		
16	The use of graphic symbols, photos and text by individuals with Rett syndrome should be acknowledged as potentially communicative.	Strongly agree	32/35 (91.4%)
17	Goals for developing or maintaining use of graphic symbols, photos and text are appropriate for individuals with Rett syndrome.	Strongly agree	29/34 (85.3%)

Goals – Aided AAC	Aided AAC		
1	It is extremely important for an individual to have more than one AAC system or device so that they can be used in different situations/settings (e.g. an eye gaze device indoors and a symbol chart outdoors).	Extremely important	32/36 (88.9%)
2	A low-tech AAC system should always be available as a back-up for any individual who has a high-tech AAC system.	Strongly agree	34/35 (97.1%)
3	An individual can be presented with two different AAC systems at the same time, or asked to use more than one system at a time.	Agree	29/33 (87.9%)
4	The same device can be used for communication and learning activities (e.g. for accessing the curriculum in school) as long as the individual is still able to access their full vocabulary.	Strongly agree	28/32 (87.5%)
5	The individual with Rett syndrome, their communication partner and the aided AAC device should be positioned in a way to maximize joint attention in the communicative interaction.	Strongly agree	31/33 (93.9%)
6	Aided AAC can be used with individuals who are ambulatory. Portability is one important consideration when choosing an aided AAC system.	Strongly agree	32/34 (94.1%)
7	Ambulatory individuals should also be provided with access to their aided AAC system when seated, for example, at mealtimes.	Strongly agree	33/34 (97.1%)
8	Aided AAC can be introduced and used successfully in adulthood.	Strongly agree	30/34 (88.2%)
9	Organization of an AAC system affects the individual's ability to communicate effectively and efficiently. It plays a role in language learning and development, and it needs to be customized and modified over time.	Strongly agree	31/33 (93.9%)
10	Vocabulary can be organized according to semantic category in aided AAC.	Agree	26/27 (96.3%)
11	Visual scene displays can be used as a starting point for aided AAC.	Agree	23/27 (85.2%)
12	Activity grids (designed for a specific activity) can be used as a starting point for aided AAC.	Agree	27/28 (96.4%)

13	Activity grids can increase participation and syntactic development by encouraging use of multiword combinations.	Agree	18/22 (81.8%)
14	Context-based grids (similar to activity grids but designed for a specific context or environment) allow for greater generalization than vocabulary designed around a single, specific activity.	Strongly agree	18/23 (78.3%)
Goals – Access	Developing And Using Different Access Methods		
1	Choice of access method can vary according to the individual's abilities at a given moment, type of aided AAC and context.	Strongly agree	32/33 (97.0%)
	Scanning		
2	Scanning can be used when individuals are unable to use direct selection to access aided AAC.	Agree	25/28 (89.3%)
3	Partner assisted scanning can be used with individuals who have developed or are developing a yes/no response and are unable to independently operate a scanning system.	Strongly agree	28/30 (93.3%)
	Direct selection		
4	Direct selection can be used when individuals have a way of directly activating aided AAC including eye gaze, touching or pointing with finger or hand, operation of a switch and/or a head pointer.	Strongly agree	32/33 (97.0%)
5	Eye gaze is usually the best way for an individual with Rett syndrome to access AAC.	Agree	33/36 (91.7%)
6	Eye gaze is not the only way for individuals with Rett syndrome to access AAC.	Strongly agree	35/36 (97.2%)
7	Individuals who are able to touch or point to access aided AAC should be encouraged to use this access method as long as it does not limit the variety and complexity of their communication.	Agree	31/33 (93.9%)

8	A head pointer could be considered when other access methods are not available or effective.	Agree	30/33 (90.9%)
	Eye Gaze		
9	An eye gaze board such as an E-tran frame can be an appropriate form of aided AAC for individuals with Rett syndrome.	Strongly agree	25/29 (86.2%)
10	Eye tracking technology such as a computer fitted with an eye tracker can be an appropriate form of aided AAC for individuals with Rett syndrome.	Strongly agree	32/32 (100%)
11	Eye tracking technology can be used with individuals who are ambulatory. Strategies to support ambulatory individuals in using eye tracking technology include positioning the device on a wall or table or in another area which the individual is able to access consistently.	Strongly agree	30/33 (90.9%)
12	Eye tracking technology can usually be used with individuals who wear glasses. If there is a problem, consider trying frameless glasses or non-reflective lenses.	Strongly agree	27/28 (96.4%)
13	Eye tracking technology can be used with individuals who have difficulties with controlling head movements when their body and head are appropriately supported and when the device is appropriately positioned.	Strongly agree	27/29 (93.1%)
Goals – Reading & Writing	Reading And Writing		
1	Reading stories together is an activity that is appropriate for all individuals with Rett syndrome to develop language, communication and literacy skills.	Strongly agree	31/34 (91.2%)
2	Most individuals with Rett syndrome should be exposed to activities to develop phonemic awareness.	Strongly agree	26/33 (78.8%)
3	Most individuals with Rett syndrome should be exposed to activities to develop an awareness of print.	Strongly agree	24/33 (72.7%)

4	Most individuals with Rett syndrome should be exposed to activities to develop a sight vocabulary.	Agree	30/33 (90.9%)
5	Most individuals with Rett syndrome should be exposed to activities to develop writing skills. This can include 'scribbling' (with an on-screen keyboard or using Partner assisted scanning) or writing letters or words.	Agree	28/34 (82.4%)
6	Most individuals with Rett syndrome should be encouraged to create their own narratives or stories.	Agree	32/34 (94.1%)

Appendix 2

For advice only

Formal Tools for Assessment of Communication and/or Development & Tracking of Communication Goals

Recommendation / Statement no.	Recommendation / Statement	Median response	n/N (%) ⁱ
	Assessment Tools		
Assessment – Tools	The following commercially available or published assessments can be valuable tools for the assessment of communication in individuals with Rett syndrome:		
1	- Inventory of Potential Communication Acts (Sigafoos et al.)	Agree	15/15 (100%)
2	- Functional Communication Profile Revised (FCP-R) (Kleiman)	Agree	9/9 (100%)
3	- Communication Matrix (Rowland)	Agree	16/17 (94.1%)
4	- The Pragmatics Profile of Everyday Communication Skills (Dewart & Summers)	Agree	10/11 (90.9%)
5	- The Triple C: Checklist of Communication Competency (Bloomberg, West, Johnson & Iacono).	Agree	10/11 (90.9%)
6	- AAC Profile: A Continuum of Learning (Kovach)	Agree	9/10 (90%)
7	- The Student, Environment, Tasks Tools (SETT) Framework (Zabala)	Agree	8/10 (80%)
8	- Peabody Picture Vocabulary Test (now PPVT-4) (Dunn & Dunn)	Agree	11/15 (73.3%)
9	- Vineland Adaptive Behavior Scales (now Vineland-3) (Sparrow et al.)	Agree	7/10 (70%)

10	- ACETS Eye Gaze Technology Screening Checklist (Lenz & Krach).	Neither agree nor disagree	7/10 (70%)
11	- British Picture Vocabulary Scale (BPVS3) (Dunn, Dunn & Styles).	Neither agree nor disagree	9/9 (100%)
12	- Clinical Evaluation of Language Fundamentals – Preschool- 2 (CELF- Preschool- 2) (Semel, Wiig & Secord).	Neither agree nor disagree	10/13 (76.9%)
13	- Clinical Evaluation of Language Fundamentals – Fifth Edition (CELF-5) (Wiig, Semel & Secord).	Neither agree nor disagree	11/13 (84.6%)
14	- Computer Based Instruction for Low Motor Language Testing (C-BILLT) (Geytenbeek).	Neither agree nor disagree	9/10 (90%)
15	- Dynamic Assessment and Goal Grid- 2 (DAGG-2) (Clarke & Schneider, Tobii-Dynavox).	Neither agree nor disagree	9/12 (75%)
16	- Preschool Language Scale (now PLS-5) (Zimmerman, Steiner & Pond).	Neither agree nor disagree	10/12 (83.3%)
17	- Reynell Developmental Language Scales (4 th edition) (Letts, Sinka & Edwards).	Neither agree nor disagree	9/10 (90%)
18	- Test of Early Communication and Emerging Language (TECEL) (Huer).	Neither agree nor disagree	5/6 (83.3%)
19	- Talking Mats (Murphy, Cameron) (Murphy & Cameron).	Neither agree nor disagree	13/15 (86.7%)
20	- The Verbal Behavior Milestone Assessment & Placement Program (VB-MAPP) (Sundberg).	Disagree	6/6 (100%)
21	- Test of Aided-Communication Symbol Performance (TASP) (Bruno).	Disagree	6/7 (85.8%)
22	- The Brigance Inventory of Early Development (IIE III).	Disagree	5/6 (83.3%)

	Intervention Tools		
Intervention – Tools	The following tools can be used to develop and track communication goals for individuals with Rett syndrome:		
1	- The Canadian Occupational Performance Measure (COPM) (Law, Baptiste, Carswell, McColl, Polatajko & Pollock).	Agree	9/10 (90%)
2	- Goal Attainment Scaling (GAS) (Kirusek & Sherman).	Agree	14/14 (100%)

Summary

Rett syndrome is a rare neurological disease of genetic origin, attributable to a (mainly) spontaneous mutation in the gene encoding Methyl-CpG-binding Protein 2 (*MECP2*). It occurs in approximately 1 in 10-12,000 females and more rarely in males. Characteristic features include seemingly near-normal development in the early months of life followed by a period of stagnation then regression, or loss of acquired skills, such as loss of spoken language and purposeful motor skills, and development of stereotypical hand movements. Co-morbid features can include: disturbances in muscle movement and tone (dystonia, dyspraxia, ataxia), breathing irregularities, cardiovascular problems, gastro-intestinal issues, seizures that may or may not be epileptic in origin, orthopaedic problems such as curvatures in the spine (scoliosis and/or kyphosis) and reduced bone density, disruptions in sleep and sensory regulation, increased anxiety and changes in affect/mood. Rett syndrome is lifelong and may be life-limiting. It is not degenerative and many affected individuals live into adulthood, showing abilities to learn and acquire or redevelop skills post-regression.

The ability, or lack of ability, to interact successfully with people around oneself and to function as an independent and autonomous communicator in society has a major impact on quality of life and on participation and well-being. Of all the aspects of Rett syndrome that individuals and families experience, difficulties in communication are often rated as one of the biggest challenges

Applied research that seeks to increase our knowledge and understanding of the communication challenges associated with Rett syndrome, and to go some way towards ameliorating them, is vital if we are to improve quality of life for individuals with Rett syndrome.

The thesis is divided into two parts. **Part One** of the thesis (Chapters 1 – 4) sets the context of Rett syndrome as a rare disease. **Part Two** (Chapters 5 – 10) presents applied research.

Chapter 1 provides a general introduction. Within this, the World Health Organization's International Classification of Functioning, Disability and Health (ICF) model is used to illustrate how the applied research undertaken in the thesis relates to different aspects of an individual's life. Three components in particular are highlighted: 'body functions and structures', 'activities and participation', and 'environmental factors'.

Chapter 2 provides a short overview of rare disease policy and the development of initiatives to meet the needs of individuals with rare diseases in the European Union (EU), especially those stemming from Directive 2011/24/EU on the Application of Patients' Rights in Cross-Border Healthcare. Together with **Chapter 3**, it outlines the legislative requirement for the development of national plans for rare diseases, identification of national, multidisciplinary Centres of Expertise for Rare Diseases, and sharing of knowledge and resources through the creation of European Reference Networks for Rare Diseases. The

Rett Expertise Centre Netherlands-GKC is cited as an example of a single-focus rare disease Centre of Expertise.

In **Chapter 3** the implementation of EU rare disease policy is examined, with a special focus on how far (by 2015) this has impacted services for individuals with Rett syndrome. It presents data from 30 European countries, showing, for example, which countries have identified experts in Rett syndrome and have established or are developing Rett Expertise Centres. The chapter highlights the value of pan-European collaborations, with Centres of Expertise and national Rett associations and foundations having a central role to play. The wishes of parents, as expressed by the national associations and foundations during the third European Rett Syndrome Conference in Maastricht in 2013, are also voiced in the chapter. These wishes – for early diagnosis, increased understanding of the disease, and better care and support for individuals and families – underpin the research aims addressed in the remaining chapters of the thesis.

Chapter 4 explores the use of databases as a mechanism for researchers and clinicians to share and expand knowledge of rare diseases. It focuses on an exploratory study of 13 genotype-phenotype databases, using Rett syndrome as a test case. By conducting a search for five *MECP2* mutations, each database was evaluated according to FAIR principles (findability, accessibility, interoperability, and reusability). In the chapter, the positive aspects and the current shortcomings of the databases are identified and discussed, and suggestions proffered for future improvements. The special role of longitudinal population-based databases and patient registries is also highlighted. The conclusion is that well-designed and well-curated databases and registries can make a significant contribution towards improved and earlier diagnosis, research, treatment and management of rare diseases such as Rett syndrome. In order to achieve this, however, such databases must be populated by high quality, detailed and FAIR data. Centres of Expertise like the Rett Expertise Centre Netherlands-GKC are identified as having a key role in contributing to (and creating and curating) such databases.

Chapter 5 acts as an introduction to the applied research chapters that follow, with a state-of-the-art overview of communication, cognition and behaviour in individuals with Rett syndrome. In particular, this chapter describes how improved awareness and understanding of the features associated with Rett syndrome have influenced and changed thinking about cognitive potential and early communication development, later communication deficits and skills, and strategies for intervention and management of communication. The potential strength of using eye gaze for communication is also highlighted.

Chapter 6 presents a study aiming to extend understanding of Rett syndrome by identifying early communicative (pre-diagnostic) indicators. This relates to the ‘body functions’ domain of the ICF. Using retrospective video analysis, the study explored response to name

as an early marker of social reciprocity in infants with classic Rett syndrome and atypical (preserved speech variant) Rett syndrome. Clear differences between the two groups were found. Areas for future research that would strengthen the findings are suggested.

Chapters 7 and 8 aim to increase knowledge relating to one of the pre-requisites underlying use of eye gaze for communication, that is, the need for an intact oculomotor system. These chapters present a two-part exploratory study that assessed oculomotor movements (saccades, smooth pursuit, optokinetic nystagmus and vestibulo-ocular reflex) through use of traditional electronystagmography (ENG). In the study, the results of a cohort with Rett syndrome were compared with those of a neuro-typical group. Qualitative analysis of the results, as presented in **Chapter 7**, suggests that individuals with Rett syndrome appear to have an intact oculomotor system. However, difficulties with the ENG assessment are highlighted. These difficulties are examined in greater detail in **Chapter 8**, and two key factors identified: quality of attention and quality of electrode signals. Future adaptations to the testing are recommended. This study relates to the ICF domains of ‘body functions and structures’.

Chapter 9 presents a qualitative study investigating experiences of Dutch families. This relates to the ICF components of ‘activities and participation’, and ‘environmental factors as an influence on functioning and disability’. Through completing an online survey, parents of children and adults with Rett syndrome living in the Netherlands shared their experiences of eye gaze technology as a form of augmentative and alternative communication. Amongst other things, questions related to the advice, training and support that families received, measures of progress in the development of the individual’s communication skills, and ratings of parental satisfaction with both the technology and the support. The potential benefits to be gained from the technology and the need for enhanced levels of support from knowledgeable professionals are both highlighted in this chapter.

In **Chapter 10**, a project aiming to develop international guidelines for the assessment, intervention and long-term management of communication in individuals with Rett syndrome is presented. As in the previous chapter, the focus is on the ICF components of ‘activities and participation’, and ‘environmental factors’. This project combined systematic reviews of literature with surveys conducted across a broad range of parents and communication professionals from multiple countries. It is the largest project of its kind to date with 650 people from 43 countries participating. Statements and recommendations were extracted from the literature reviews and surveys, and fed through an expert panel (a Delphi process) in order to arrive at a consensus agreement on the final guidelines. The guidelines are presented in an Appendix to the thesis.

Chapter 11 is a general discussion with valorisation section. Common threads running through all of the research presented in the thesis are identified and discussed, and the

societal relevance of the studies and their implications for clinical practice, policy, and decision-making are outlined. Avenues for future research are suggested.

This thesis aims to show that applied research undertaken within the context of a Rett Expertise Centre can make a positive contribution towards understanding and addressing the communication challenges, the communication support needs, and the (hidden) communication potential of individuals with Rett syndrome. Increasing our understanding of the outward and underlying features of Rett syndrome, enhancing professional and parental knowledge and skills, and empowering professional-parent partnerships – these are all key to improving the current communication opportunities ('care for today') afforded to individuals with Rett syndrome, while simultaneously seeking a 'cure for tomorrow'.

Samenvatting

Rett syndroom is een zeldzame neurologische ontwikkelingsstoornis die in de meeste gevallen veroorzaakt wordt door een spontane mutatie in het gen dat codeert voor Methyl-CpG-bindend Proteïne 2 (MECP2). Het komt bij meisjes voor in ongeveer 1 op 10-12.000 geboortes en is bij jongens veel zeldzamer. Kenmerkend is de schijnbaar bijna normale ontwikkeling in de eerste maanden na de geboorte, gevolgd door een periode van stagnatie en regressie, met verlies van aangeleerde vaardigheden zoals spraak en zinvol handgebruik en met ontwikkeling van stereotypische handbewegingen. Bijkomende kenmerken kunnen zijn: een verstoord bewegingspatroon en afwijkende spierspanning (dystonie, dyspraxie, ataxie), een verstoorde ademhaling, cardiovasculaire problemen, maag-darm problemen, epilepsie en niet-epileptische aanvallen, skeletafwijkingen zoals vervorming van de wervelkolom (scoliose en/of kyfose) en verminderde botdichtheid, slaapstoornissen, toegenomen prikkelbaarheid en verandering in affect of stemming. Rett syndroom is levenslang en kan de levensduur beperken. Het is geen degeneratieve aandoening; velen leven tot in volwassenheid en tonen daarbij vermogen tot leren en herkrijgen of verkrijgen vaardigheden na de regressiefase.

Het vermogen, of onvermogen, om succesvol te communiceren met mensen in de omgeving en om onafhankelijk en autonoom te functioneren in de maatschappij heeft grote impact op de kwaliteit van leven en het ervaren welzijn. Van alle aspecten van de aandoening, die mensen met Rett syndroom en hun familie ervaren, wordt beperking in communicatie vaak gezien als één van de grootste uitdagingen.

Toegepaste onderzoek naar meer kennis en begrip van de uitdagingen in communicatie bij Rett syndroom en naar het verlichten van de last voor betrokkenen, is essentieel voor het verbeteren van de kwaliteit van leven voor mensen met Rett syndroom.

Dit proefschrift bestaat uit twee delen. **Het eerste deel** van het proefschrift (Hoofdstuk 1 t/m 4) presenteert Rett syndroom in de context van zeldzame ziekten. In **het tweede deel** (Hoofdstuk 5 t/m 10) wordt toegepast onderzoek gepresenteerd.

Hoofdstuk 1 is een algemene inleiding. Met het International Classification of Functioning, Disability and Health (ICF) model van de Wereld Gezondheids Organisatie wordt toegelicht hoe het toegepaste onderzoek uit dit proefschrift gerelateerd is aan de verschillende aspecten van leven van mensen met Rett syndroom. Drie aspecten zijn specifiek benadrukt: 'lichaamsfuncties/anatomische eigenschappen', 'activiteiten en participatie', en 'externe factoren'.

In **Hoofdstuk 2** wordt een kort overzicht gegeven van zeldzame ziekten beleid en het ontwikkelen van initiatieven ten behoeve van de noden van mensen met zeldzame ziekten in de Europese Unie, met name de initiatieven die voortkomen uit Richtlijn 2011/24/EU betreffende de toepassing van de rechten van patiënten bij grensoverschrijdende gezondheidszorg. Samen met **Hoofdstuk 3** schetst het wetgevende voorwaarden voor het ontwikkelen van nationale projecten voor zeldzame ziekten, voor (h)erkenning van

ationale multidisciplinaire expertisecentra voor zeldzame ziekten, en voor het delen van kennis en middelen door het vormen van Europese referentienetwerken voor zeldzame ziekten. Het Rett Expertise Centrum Nederland-GKC wordt besproken als voorbeeld van een expertisecentrum met de focus op één zeldzame ziekte.

In **Hoofdstuk 3** wordt onderzoek beschreven naar de implementatie van het EU zeldzame ziekten beleid, met speciale focus op de mate waarin dit (in 2015) impact had op de dienstverlening aan mensen met Rett syndroom. Gegevens uit 30 Europese landen worden beschreven. Hieruit blijkt bijvoorbeeld welke landen specifieke experts op het gebied van Rett syndroom hadden en welke landen een Rett expertisecentrum hadden of hieraan werkten. Dit hoofdstuk benadrukt de waarde van Europese samenwerking, waarin Rett expertisecentra en nationale Rett verenigingen en fondsen een centrale rol spelen. Ook worden de wensen van ouders besproken in dit hoofdstuk, zoals door de nationale verenigingen en fondsen gepresenteerde tijdens het derde Europese Rett Congres te Maastricht in 2013. Deze wensen – een vroege diagnose, meer kennis over de aandoening, betere zorg en ondersteuning van mensen met Rett syndroom en hun familie – vormen de basis voor de onderzoeksdoelen van de volgende hoofdstukken van dit proefschrift.

In **Hoofdstuk 4** wordt het gebruik van databases onderzocht als een middel om gegevens over zeldzame ziekten te delen en kennis te vergroten. Een verkennend onderzoek naar 13 genotype-fenotype databases, met Rett syndroom als test casus, wordt beschreven. Gebruikmakend van een zoekopdracht voor vijf MECP2 mutaties, werden verschillende databases beoordeeld volgens het FAIR-principe (Findability, Accessibility, Interoperability and Reusability resp. vindbaarheid, toegankelijkheid, onderlinge uitwisselbaarheid en herbruikbaarheid). In dit hoofdstuk worden zowel de positieve aspecten als de tekortkomingen van de databases besproken en suggesties gedaan voor verbetering. Ook wordt de speciale rol van databases op basis van bevolkings- en patiëntenregisters benadrukt. De conclusie is dat goed ontworpen en goed onderhouden databases en registers een significante bijdrage kunnen leveren aan verbetering van vroege diagnostiek, onderzoek, behandeling en beleid bij zeldzame ziekten zoals Rett syndroom. Om dit te bereiken, dienen deze databases gevuld te zijn met nauwkeurige en FAIR-data. Vastgesteld werd dat expertisecentra zoals het Rett Expertise Centrum Nederland-GKC een belangrijke rol spelen in het bijdragen aan (en creëren en beheren van) dergelijke databases.

Hoofdstuk 5 is een inleiding voor het toegepast onderzoek verricht binnen het kader van dit proefschrift. Daarbij wordt een state-of-the-art overzicht gegeven van communicatie, cognitie en gedrag bij mensen met Rett syndroom. In dit hoofdstuk wordt in het bijzonder beschreven hoe toegenomen bewustzijn en begrip van de kenmerken van Rett syndroom invloed hebben gehad op het denken over cognitief vermogen en vroege communicatieontwikkeling, op latere communicatievaardigheden en –beperkingen en op

behandelstrategieën en interventies voor communicatie. Ook wordt ingegaan op de mogelijkheid en doelmatigheid van het gebruik van oogbesturing.

In **Hoofdstuk 6** wordt een onderzoek beschreven naar het verbeteren van kennis en begrip van aspecten van Rett syndroom door het vaststellen van vroege (pre-diagnostische) communicatie-indicatoren. Dit vanuit het perspectief van het domein 'lichaamsfuncties' van de ICF. Gebruikmakend van retrospectieve video analyse, is reactie op de naam zeggen onderzocht als een vroeg teken van sociale wederkerigheid bij kinderen met klassiek Rett syndroom en atypisch Rett syndroom (variant met behouden spraak). Duidelijke verschillen werden tussen de twee groepen gevonden. Mogelijk vervolgonderzoek naar deze verschillen wordt besproken.

Hoofdstukken 7 en 8 zijn gericht op het verbeteren van kennis over één van de voorwaarden voor het gebruik van oogbesturing voor communicatie; de noodzaak van een intact oculomotorisch systeem. In deze hoofdstukken wordt een tweedelige exploratieve studie beschreven over assessment van oogbewegingen (saccades, volgbeweging, optokinetisch nystagmus en vestibulo-oculaire reflex), gebruikmakend van traditionele electronystagmografie (ENG). In deze studie zijn resultaten van een cohort met Rett syndroom vergeleken met die van een neurotypische groep. Kwalitatieve analyse van de resultaten in **hoofdstuk 7** laat zien dat mensen met Rett syndroom een intact oculomotorisch systeem blijken te hebben. De belemmeringen met ENG-assessment werden toegelicht en verder onderzocht in **hoofdstuk 8**. In het bijzonder ging de aandacht uit naar twee factoren: de kwaliteit van de aandacht en de kwaliteit van het signaal van de elektroden. Aanbevelingen voor toekomstige aanpassingen worden gegeven. Dit onderzoek betreft het domein 'lichaamsfuncties/anatomische eigenschappen' van de ICF.

In **Hoofdstuk 9** wordt een kwalitatief onderzoek naar ervaringen van Nederlandse families gepresenteerd. Dit is gerelateerd aan de ICF-domeinen 'activiteiten en participatie' en 'externe factoren van invloed op het functioneren en de beperkingen'. Door middel van een online-enquête deelden Nederlandse ouders van kinderen en volwassenen met Rett syndroom hun ervaringen met oogbesturingstechnologie voor ondersteunde communicatie. Onder andere betreffen de vragen advies, training en ondersteuning die ouders kregen, het meten van vorderingen in de ontwikkeling van communicatievaardigheden en de beoordeling van tevredenheid van ouders met zowel de technologie als de ondersteuning. De voordelen die met deze techniek kunnen worden behaald en de behoefte aan meer ondersteuning van deskundige professionals worden toegelicht.

In **Hoofdstuk 10** wordt een onderzoek naar de ontwikkeling van internationale richtlijnen voor assessment, interventie en lange termijn behandeling van communicatie bij mensen met Rett syndroom beschreven. Net als in het voorgaande hoofdstuk is hier de focus op ICF-domeinen 'activiteiten en participatie' en 'externe factoren'. In dit project is een combinatie gemaakt van systematische reviews van de literatuur en enquêtes onder een

brede groep ouders en communicatie-professionals uit vele landen. Het is het grootste project in z'n soort tot heden met 650 mensen uit 43 landen. Uit de literatuuroverzichten en enquêtes werden stellingen en aanbevelingen verkregen, die aan een expert panel zijn voorgelegd (een Delphi proces) om tot een consensus te komen voor de uiteindelijke richtlijnen. De richtlijnen zijn weergegeven in de appendix bij dit proefschrift.

Hoofdstuk 11 is de algemene discussie met inbegrip van de valorisatie. Hier worden de bevindingen van alle studies besproken. Het verricht onderzoek wordt bediscussieerd en de maatschappelijke relevantie van de bevindingen en de implicaties voor toepassing in behandeling, beleid en besluitvorming worden uiteengezet. Mogelijkheden voor vervolgonderzoek komen aan de orde.

Met dit proefschrift is beoogd aan te geven dat toegepast onderzoek, uitgevoerd binnen een Rett Expertise Centrum, een belangrijke bijdrage kan leveren aan begrip en aanpak van de uitdagingen in communicatie, de behoefte aan ondersteuning daarbij en het niet altijd direct zichtbare vermogen tot communicatie van mensen met Rett syndroom. Zowel toename van ons begrip van de kenmerken en onderliggende aspecten van Rett syndroom, als het verbreden en verdiepen van kennis en vaardigheden van professionals en ouders, alsook het versterken van samenwerking tussen professionals en ouders, zijn essentieel in het verbeteren van mogelijkheden voor communicatie die momenteel ('care for today') geboden worden aan mensen met Rett syndroom, terwijl wij zoeken naar een 'cure for tomorrow'.

Many thanks to Mariëlle van den Berg for assisting with this translation.
Mariëlle, hartelijk bedankt!

List of Publications

Peer-Reviewed Publications

1. * **Townend G.S.**, Bartolotta T.E., Urbanowicz A., Wandin H., Curfs L.M.G. International clinical guidelines for management of communication in individuals with Rett syndrome. Submitted December 2018.
2. * de Breet L.[#], **Townend G.S.**[#], Curfs L.M.G., Kingma H., Smeets E., Widdershoven J., van de Berg R. (2019). Challenges in evaluating the oculomotor function in individuals with Rett syndrome using electronystagmography. *European Journal of Paediatric Neurology*, 23(2), 262-269. ([#]shared first authorship)
3. * **Townend G.S.**, van de Berg R., de Breet L., Hiemstra M., Wagter L., Smeets E., Widdershoven J., Kingma H., Curfs L.M.G. (2018). Oculomotor function in individuals with Rett syndrome. *Pediatric Neurology*, 88, 48-58.
4. * **Townend G.S.**[#], Ehrhart F.[#], van Kranen H.J., Wilkinson M., Jacobsen A., Roos M., Willighagen E.L., van Enckevort D., Evelo C.T., Curfs L.M.G. (2018). MECP2 variation in Rett syndrome – an overview of current coverage of genetic and phenotype data within existing databases. *Human Genetics*. 39(9), 14–924. ([#]shared first authorship)
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10. * **Townend G.S.**, van Kranen H.J., van der Stel R., van den Berg M., Smeets E., van Waardenburg D., Curfs L.M.G. (2015). Rett syndrome as a rare disease: a European perspective. *Public Health Genomics*. 18(4), 233-6.
11. Judge, S., & **Townend, G.** (2013). Perceptions of the design of voice output communication aids. *International Journal of Language & Communication Disorders*, 48(4), 366-381.

Book Chapters, Reports and Conference Proceedings

1. * **Townend G.S.**, Marschik P.B., Kaufmann W., Fabio R.A., Sigafos J., Curfs L.M.G. (2017). Cognition, behavior and communication. In Kaufmann WE. (ed.) *Rett syndrome*. Ch.5, 50-61. London: Mac Keith Press.
2. Williams K., Keeley T., Malmén M., Phelps H., Jordan P., Anand R., Kaminsky S., Bartolotta T., Curfs L., Kaufmann W., Mariotti O., Neul J., Nues P., Percy A.K., Sharma G., **Townend, G.** (2017). Burden of disease in Rett syndrome: a qualitative analysis and development of a conceptual model. *Value in Health*, 20(5), A226-A226.
3. **Townend, G.S.**, Smeets, E., Marschik P.B., Curfs L.M.G. (2016). Communication in Individuals with Rett Syndrome: What we know now and what we have yet to find out. *Wiener Medizinische Wochenschrift*. 166(11), 371-374.
4. **Townend, G.**, Roentgen, U., Dalemans, R., Witte de, L. (2014). *Wegwijzer Ondersteunde Communicatie*. Final project report. Heerlen: HSZuyd/EIZT
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7. **Townend, G.** (2007). I want this one! Is it possible to formalize the decision-making process when comparing communication aids on trial loan? *Communication Matters*, 21(1), 35-38.

Publications marked with * are included in this thesis.

Curriculum Vitae

Gillian Suzanne Townend (née Leather) was born in Widnes, Cheshire (UK) in February 1967. She studied Speech Science at Sheffield University from 1985 – 1989, and was awarded an upper second class B.Med.Sci. (Speech) (Hons) alongside being granted her Licence to Practice by the College of Speech Therapists. In 1996 she was awarded an M.Phil. (by own research) from Sheffield University, for a thesis entitled: *A comparison between factors which may facilitate communication in adults with severe learning disabilities in different workplace settings*. She continues to be a registered member of the Royal College of Speech and Language Therapists and the UK Health Professions Council, and is a BROK® certified clinical investigator.

Gill is a Speech and Language Therapist with longstanding clinical and research experience, particularly in the field of Augmentative and Alternative Communication (AAC). She worked in the UK for 20 years, with children and adults with congenital/developmental disabilities and adults with acquired disorders before moving to the Netherlands 11 years ago. Since then she has worked as a researcher within the Devices for Dignity Healthcare Technology Cooperative in the UK, as joint lead of a national project evaluating users' perceptions of communication aid design, and at the Expertisecentrum voor Innovatieve Zorg en Technologie (Technology in Care) at Zuyd University of Applied Sciences in Heerlen, The Netherlands, where she co-produced a *Wegwijzer Ondersteunde Communicatie* (roadmap to AAC supports and services in the Netherlands).

Since 2013, Gill has been a researcher at the Rett Expertise Centre Netherlands-GKC, Maastricht University Medical Centre (MUMC+) and since, the summer of 2018, has also been working for Rett UK, as joint lead of their Communication and Education Support Project. She currently divides her time between the two countries.

She is a co-founder and joint coordinator of two national Networks for Speech and Language Therapists working with individuals with Rett syndrome, one in the Netherlands and one in the UK, and a similar network for physiotherapists in the Netherlands. She is also working with colleagues to develop communication support groups for parents and caregivers, and piloting 'out and about' communication groups for individuals with Rett syndrome and their families in both countries. Gill has close connections with all of the European Rett Associations; she is the UK and European representative on the North American Rett Clinics Network and a member of the advisory board for the international Burden of Illness Study. Since 2016, she has been leading the Rettsyndrome.org-funded international project to develop clinical guidelines for the assessment, intervention and long-term management of communication in individuals with Rett syndrome. The project is nearing completion and a guidelines handbook is due to be published in 2019.

In addition to the guidelines project team, which includes colleagues from the US, Sweden and Australia, Gill has developed research collaborations with teams at iDN @ Göttingen and Graz and the Karolinska Institutet, University College London, the Otorhinolaryngology Department at MUMC+, and with her colleagues at the Rett Expertise Centre Netherlands-GKC and Rett UK.

Her current research interests include:

- Development of clinical guidelines for the management of communication in individuals with Rett syndrome;
- Eye tracking in individuals with Rett syndrome and the functional use of eye gaze for communication;
- Development of alternative methodologies for assessing language and cognition in individuals with Rett syndrome;
- Early (pre-diagnosis) communication development in individuals with typical and atypical Rett syndrome;
- European policy in relation to rare diseases and its implications for Rett syndrome; and,
- The establishment of clinical and research-based networks and collaborations both within and outside of Europe.

Acknowledgements

One of the good things about writing a PhD at my age and at this stage in my career, is the opportunity to thank the many people who have helped me along the way. Some people I have known for many years and some for a much shorter time, but to each I owe a debt of gratitude. The list that follows is not exhaustive and I apologise to anyone I may have missed.

Were it not for a chance meeting at a Burns Night Supper in 2013, this thesis would not exist. In fact, it is more than likely that I would not have been introduced to the world of Rett syndrome at all, and would not have had the opportunity to channel my curiosity, my energy and my previous professional knowledge and skills into this area of research and clinical practice in the six years since then. So, my first thanks must go to the unknown person who so judiciously arranged the table settings on that evening and sat me next to Prof. dr. Leopold Curfs. A meeting of pure serendipity, and the rest, as they say, is history! Many, many thanks Leopold for having the wisdom and perception to see the potential fit between my experience and the (at that time) new but expanding team at the Rett Expertise Centre, for inviting me to join you, and for encouraging me to create my own path within this Rett syndrome world since then. Thank you for your ongoing support and belief in my abilities, for inspiring and guiding me through this PhD in your role as both mentor and supervisor, and continuing to offer me opportunities to develop and grow. Thank you, too, for having a vision that is not hindered by narrow boundaries and that has allowed me to explore and develop my knowledge of many aspects associated with rare diseases in general and Rett syndrome in particular. Many thanks, too, to Rob van der Stel and Nathalie Bouwman from Stichting Terre (Dutch Rett Syndrome Foundation) for putting your trust in Leopold's judgement and for providing the financial support that enabled me to get started in my new role. I am also indebted to Mariëlle van den Berg and Ad Linssen, and other members of the board of the NRSV (Dutch Rett Syndrome Association) who have since picked up that mantle and who provide the ongoing financial support that has allowed me to continue, has allowed me to thrive and to develop and expand my role within the Rett Expertise Centre Netherlands-GKC. Thank you for this.

As soon as I began working at the Rett Expertise Centre in March 2013 I was plunged into arranging the 'communication track' of the European Rett Syndrome Conference that was to be held in Maastricht later that year. This immersion was invaluable in getting to know and build relationships with researchers, clinicians and parents from across Europe, the USA and Australia, relationships that I continue to be grateful for and to value highly. From the conference, collaborations and friendships were established, such as that with Dr. Peter Marschik and his team in Graz. Thank you Peter for your ongoing support and encouragement, and for acting as co-supervisor for my PhD. I look forward to continued opportunities for joint working. Also through the conference I met Dr. Theresa Bartolotta (Monmouth University, NJ), Dr. Anna Urbanowicz (RMIT University, Melbourne) and Helena Wandin (Swedish National Center for Rett Syndrome and Related Disorders, and Uppsala University), all of whom I am proud to call both friends and colleagues, and with

whom I have had the great pleasure of working closely on the guidelines project in recent years. I have benefitted enormously from the many hours we have spent together via video-conference (albeit that at least one of us is always bleary-eyed as we navigate the very wide span of time zones), as well as the opportunities we have had to meet together in person. Thank you, too, to Sally-Ann Garrett for first stimulating the discussions at the conference that led to the formation of the guidelines project, and for being an initial member of the project team. And special thanks to Paige Nues and others at Rettsyndrome.org, whom I also first met at the conference in Maastricht, for the financial support provided by Rettsyndrome.org that enabled the guidelines project to become a reality.

The Rett Expertise Centre has grown since I joined in 2013. I have been fortunate to be joined by Gerna Scholte and Hanneke Borst so that we have become the ‘applied research group’. What a wonderful opportunity this has afforded me to develop both the research and clinical support sides of my work in the Netherlands as we have worked together to form, amongst other things, the Dutch networks for speech and language therapists and, more recently, for physiotherapists, and as we continue to explore ideas for paramedical and neurohabilitation research and intervention together. Thank you Gerna and Hanneke for your enthusiasm, dedication and hard work. I have also been joined by colleagues who form the ‘basic research group’ and the patient care team of the Rett Expertise Centre, and I have established collaborations with other colleagues within Maastricht University Medical Centre. Thank you to Dr. Frederique Erhart and Nasim Sangani. You have helped me to understand something of the biological and molecular aspects of Rett syndrome, and to you, Dr. Henk van Kranen, for sharing your knowledge of genetics. Thank you to Prof. dr. Herman Kingma, Dr. Raymond van de Berg, and Dr. Josine Widdershoven (Balance Division, ENT Dept, MUMC+) for encouraging my interest in eye gaze and helping me to understand the mechanisms underlying this. And heartfelt thanks to Dr. Eric Smeets, who together with Prof. dr. Leopold Curfs was one of the founding fathers of the Rett Expertise Centre. Your knowledge and understanding of Rett syndrome, and your compassion and commitment to the many families with whom you have worked, have been inspirational as I have worked to establish a place for myself within this community. Also thanks to Dr. Dick van Waardenburg (Head of PICU, MUMC+) for introducing me to the mesmerising but fascinating field of brainstem physiology and the autonomic nervous system.

Thank you to all of my co-authors, both those on the papers included in this thesis and those on papers not included here but still an important part of my body of work. Without you there would be no PhD. And of course, my grateful thanks are extended to the members of the assessment committee who have passed judgement on my thesis. To the chair, Prof. dr. Luc Zimmermann, and to Prof. dr. Boris Kramer and Prof. dr. Lodewijk van Rhijn (all at MUMC+), to Dr. Anne-Marie Bisgaard (Danish Rett Centre, Rigshospitalet) and Prof. dr. Alexander von Gontard (Saarland University Hospital) – many, many thanks.

Over the last year I have been privileged to be able to work for Rett UK as well as for the Rett Expertise Centre Netherlands-GKC. I am grateful for this opportunity to work across two countries, an opportunity that allows me to develop and experience the reality of cross-country collaboration, and to use each place as a fertile testing ground for research and models of intervention and family support. Life is certainly never dull; it is always interesting, always busy, always rewarding! To Becky Jenner and the trustees of Rett UK, thank you for your support and confidence in me, and to Callie Ward and Abigail Davison-Hoult I have to say a big thank you for being such wonderful colleagues. To have good colleagues in one job, one country, is a blessing; to have found them in two jobs and two countries is beyond price. Callie and Gerna, your unending enthusiasm and quest to support, facilitate and advocate for people with Rett syndrome and to make sure that everyone believes in the potential and ability of those individuals is infectious. To Abigail, Becky, Paige and Mariëlle, to Klaartje van Schijndel and Yolande van Boven, to Liz Campbell, and to all the other parents of individuals with Rett syndrome whom I am fortunate to know, in the Netherlands, in the UK, in the US, and around the world, I can only say that I am constantly overwhelmed by your boundless energy and unswerving commitment to your children, to improving their communication and education opportunities, their quality of life, and opening up their life chances. You are also my inspirations.

Of course, none of the work I do now nor the research I have undertaken for my PhD could have taken place without my background in speech and language therapy. For this I must thank first of all my mum. You, mum, planted in my mind the idea of speech therapy as a career when I was aged 14. I hope that you are happy with the choices I have made and where they have taken me as a result of your suggestion! Having chosen speech therapy as a career I was fortunate as a student to have a placement in my final year with Kath Williamson. Perhaps neither of us foresaw then the lifelong friendship that would develop, nor the job-share we would later undertake (still early in my career) that set me on the path I was to take, fostering in me a motivation and a heart for working with people with complex communication needs. Kath, your work ethic and your enquiring mind are unsurpassed. You have been my role model throughout my career and I miss having you nearby. To Alison Mackenzie, another Sheffield colleague and lifelong friend, I also owe a debt of gratitude. Your enthusiasm and your commitment to augmentative and alternative communication has also shaped and inspired me. To Kath and Alison, a big thank you.

Finally, of course, I could do none of what I do without the love and support of friends and family. To my mum and dad (Judith and Neville), my sister and brother (Vicky and Nick), thank you for providing a supportive and loving home in my childhood, and for your continuing love and support to the present day. To my parents-in-law and sister-in-law (Margaret, Roy and Sarah) thank you for your love and support throughout my adult life. To Jessica and Frank, forever to be known as my 'Dutch-American neighbours', thank you for the support you have given me and my family over the last ten years. Knowing you were close at hand has been both a reassurance and a joy, for me and David, and for the girls.

To Alice and Lottie, my wonderful paranympths, I love you more than words can say and am proud of you as my daughters and the fine young women you are. Thank you for putting up with the long hours I have worked and all the travelling I do. And last, but by no means least, to David whom I first knew at the age of four. Since meeting again at university, you have been there beside me. For more than 30 years, you have supported me and encouraged me to believe in myself; you have been a sounding board when I have needed one, you have offered advice and guidance (which I have not always received as graciously as I should) and shown me paths through the maze, and you have always fought my corner when I have needed it. Thank you for being there for me.

This thesis is dedicated to my family and to all of the families of individuals with Rett syndrome whom I know. You give reason and purpose to who I am and to what I do.

Thank you.