# Rett Syndrome

# 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 unaided[8] or aided[9] 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.