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Communication: How do females with Rett syndrome perform this activity and what factors influence performance?

Anna Urbanowicz, BSc (OT) (Hons)

School of Medical and Health Sciences

Edith Cowan University

Telethon Kids Institute

The University of Western Australia

This thesis is presented for the award of Doctor of Philosophy

October 2016

USE OF THESIS

The Use of Thesis statement is not included in this version of the thesis.

Declaration

I certify that this thesis does not, to the best of my knowledge and belief:

i. incorporate without acknowledgement any material previously submitted for a degree or diploma in any institution of higher education;

ii. contain any material previously published or written by another person expect where due reference is made in the text of this thesis; or

iii. contain any defamatory material.

This thesis contains published work and work prepared for publication, some of which has been co-authored. The bibliographical details of published work are presented at the beginning of the relevant chapter.

The work involved in designing the studies described in this thesis was performed primarily by Anna Urbanowicz (the candidate). The thesis outline and experimental design was planned and developed by the candidate in consultation with Associate Professor Sonya Girdler, Associate Professor Natalie Ciccone, Dr Jenny Downs and Associate Professor Helen Leonard (the candidate's supervisors).

The candidate was responsible for collecting qualitative data for the first study presented in this thesis and all data management and data analysis. Data from the Australian Rett Syndrome Database and International Rett Syndrome Phenotype Database were used in the remaining three studies presented in this thesis. The candidate drafted the original thesis with the candidate's supervisors providing feedback on drafts until the examinable version was finalised.

Candidate signature:

Primary supervisor signature:

Abstract

Background

Rett syndrome is a neurodevelopmental disorder primarily caused by mutations in the X-linked *methyl-Cp2G-binding protein 2 (MECP2)* gene. The disorder affects approximately 1 in 9000 females and is usually associated with language, physical and intellectual impairments, each of which contributes to difficulties with communication. In Rett syndrome, eye gaze is considered a common form of communication and conventional methods, such as talking and gestures, less common. Females appear to use these forms of communication to serve a number of functions including choice making, requesting, social convention, bringing attention to themselves, and to reject, comment and answer. However, the literature is limited due to poorly described case inclusion criteria, the inclusion of cases without a diagnosis of Rett syndrome and small sample sizes. Furthermore, there is a paucity of research on the numerous barriers and facilitators to successful communication. Therefore the aim of this research was to describe the performance of communication tasks in girls and women with Rett syndrome and to investigate factors that are positively and negatively associated with performance.

Methods

Qualitative and quantitative methods were used to understand the communication performance of girls and women with Rett syndrome and the impairments of body function and structure, activity limitations and contextual factors that influence these. The International Classification of Functioning Disability and Health - Child and Youth Version (ICF-CY) and The Communication Matrix were used as the theoretical framework throughout the research. This thesis includes four studies of which the first employed interviews with caregivers, the second and third used caregiver questionnaire data and the final utilised video data of girls and women engaged in a communicative interaction. Data were used to describe the use of specific communication modalities such as eye gaze, gestures and speech, and communicative functions including the ability to make requests and choices. Relationships between the performance of these communication tasks and factors including *MECP2* mutation type, age and level of motor abilities were investigated.

Results

During interviews all parents reported their daughters were able to express discomfort and pleasure, and make requests and choices using a variety of modalities including body movements and eye gaze. They also reported level of functional abilities and environmental factors influenced communication performance. Questionnaire data on speech-language

abilities showed 89% (685/766) acquired speech-language abilities in the form of babble or words at some point in time. Of those who acquired babble or words, 85% (581/685) experienced a regression in these abilities. Those with a p.Arg133Cys mutation were the most likely to use one or more words, prior to (RRR=3.45; 95% CI 1.15-10.41) and after (RRR=5.99; 95% CI 2.00-17.92) speech-language regression. Australian questionnaire data (n=151) found women aged 19 years or older had the lowest scores for eye gaze. Females with better gross motor abilities had higher scores for the use of eye gaze and gestures. The use of eye gaze did not vary across mutation groups, but those with a C-terminal deletion had the highest scores for use of gestures. The video study found 82.8% (53/64) of the sample made a choice, most using eye gaze. Of those who made a choice, 50% did so within 8 seconds.

Conclusions

In using qualitative and quantitative methods, and the ICF-CY and The Communication Matrix as the theoretical framework, this thesis was able to provide new insight into the way in which females with Rett syndrome communicate while considering the influence of impairments of body function and structure, activity limitations and contextual factors. We found that females with Rett syndrome share communicative strengths including the use of eye gaze and the ability to make choices. Multidisciplinary assessment of communication abilities, considering the range of factors identified to impact communication, and using multiple sources of information, will likely result in a more accurate assessment of the communication abilities of girls and women with Rett syndrome. Interventions should target communicative strengths, such as the use of eye gaze, and factors shown to impact communication, including the skills of communication partners. Reporting and accounting for genetic information in future research would help improve our understanding of the relationship between *MECP2* and communication abilities, which may in turn improve our knowledge of the role *MECP2* plays in neurodevelopment.

Acknowledgements

To my supervisors Associate Professor Sonya Girdler, Associate Professor Natalie Ciccone, Dr Jenny Downs and Associate Professor Helen Leonard, thank you for your unique contributions and making this research a reality. Sonya, for inspiring me as a young honours student to tackle research, for your continued support throughout this PhD and for contributing your occupational therapy perspective; Natalie, for boosting my morale when it was needed the most and for your expertise in speech-language pathology; Jenny, for always being available to answer my questions and for your knowledge of physiotherapy and Rett syndrome; and Helen, for driving the Rett syndrome research agenda in Australia for over 20 years and ultimately making this research possible, your passion for making a difference to the lives of those affected by Rett syndrome is unparalleled. I would also like to thank Ms Ami Bebbington and Mr Peter Jacoby for their statistical wisdom and support.

I gratefully acknowledge the contribution of families participating in the Australian Rett Syndrome Database and the International Rett Syndrome Phenotype Database who provided data for this research. Their time and effort taken to complete questionnaires, video their daughters and participate in interviews is greatly appreciated. Ultimately it is their ongoing support of Rett syndrome research that has allowed this thesis, which has led to improved knowledge on communication abilities in Rett syndrome, to be completed.

I also extend a big thank you to the Australian Paediatric Surveillance Unit, the Rett Syndrome Association of Australia and the many community-based clinicians for continuing to facilitate the ascertainment of Australian cases of Rett syndrome. I would also like to recognise the financial support of the Australian Postgraduate Award, and the Stan and Jean Perron Top-Up Scholarship.

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List of publications

Chapter four

Urbanowicz, A., Leonard, H., Girdler, S., Ciccone, N., & Downs, J. (2016). Parental perspectives on the communication abilities of their daughters with Rett syndrome. *Developmental Neurorehabilitation, 19*(1), 17-25. doi: 10.3109/17518423.2013.879940

Chapter five

Urbanowicz, A., Downs, J., Girdler, S., Ciccone, N., & Leonard, H. (2014) Aspects of speech-language abilities are influenced by *MECP2* mutation type in girls with Rett syndrome. *American Journal of Medical Genetics: Part A, 9999,* 1-9. doi: 10.1002/ajmg.a.36871

Chapter six

Urbanowicz, A., Downs, J., Girdler, S., Ciccone, N., & Leonard, H. (in press). An exploration of the use of eye gaze and gestures in females with Rett syndrome. *Journal of Speech, Language, and Hearing Research.*

Chapter seven

Urbanowicz, A., Ciccone, N., Girdler, S., Leonard, H., & Downs, J. (under review). Choice making in Rett syndrome: A descriptive study using video data. *Disability and Rehabilitation.*

Conference presentations

Urbanowicz, A., Girdler, S., Ciccone, N., Downs, J., & Leonard, H. (September 2016) *How do females with Rett syndrome communicate and what factors influence successful communication?* International Rett Syndrome Conference RTT 50.1, Vienna, Austria (Oral presentation)

Urbanowicz, A., Ciccone, N., Downs, J., Girdler, S., & Leonard, H. (August 2016) *Choice making in Rett syndrome: A descriptive study using video data.* 15th World Congress of the International Association for the Scientific Study of Intellectual and Developmental Disabilities (IASSIDD), Melbourne, Australia (Oral presentation)

Urbanowicz, A., Downs, J., Girdler, S., Ciccone, N., Leonard, H. (August 2016) *An exploration of the use of eye gaze and gestures in female with Rett syndrome.* 15th World Congress of the International Association for the Scientific Study of Intellectual and Developmental Disabilities (IASSIDD), Melbourne, Australia (Oral presentation)

Urbanowicz, A., Leonard, H., Girdler, S., Ciccone, N., & Downs, J. (November 2014) *How can parental perspectives inform research into the communication abilities of those with intellectual disability? An example from Rett syndrome.* 49th Annual Australasian Society of Intellectual Disability (ASID) Conference, Fremantle, Western Australia, Australia (Oral presentation)

Urbanowicz, A., Girdler, S., Downs, J., Ciccone, N., & Leonard, H. (June 2014) *Learning from the perspectives of parents on the communication abilities of their daughter with Rett syndrome.* 16th International Congress of the World Federation of Occupational Therapists, Yokohama, Japan (Oral presentation)

Urbanowicz A., Downs, J., Girdler, S., Ciccone, N., & Leonard, H. (October 2013) *Speech and language abilities before and after regression in 1011 girls and women with Rett syndrome.* 3rd European Rett Syndrome Conference, Maastricht, The Netherlands (Oral presentation)

Urbanowicz, A., Girdler, S., Downs, J., Ciccone, N., & Leonard, H. (October 2013) *What can we learn from the perspectives of mothers on the communication abilities of their daughter with Rett syndrome?* 3rd European Rett Syndrome Conference, Maastricht, The Netherlands (Poster presentation)

Urbanowicz, A., Girdler, S., Downs, J., Ciccone, N., & Leonard, H. (October 2013) *Expressive communication abilities of Australian girls and women with Rett syndrome.* 3rd European Rett Syndrome Conference, Maastricht, The Netherlands (Poster presentation)

Urbanowicz, A., Girdler, S., Ciccone, N., Downs, J., & Leonard, H. (October 2012) *Communication abilities in girls and women with Rett syndrome.* Child & Adolescent Health Research Symposium, Telethon Kids Institute, Perth, Western Australia & Princess Margaret Hospital for Children, Perth, Western Australia, Australia (Oral presentation)

Urbanowicz, A., Girdler, S., Downs, J., Ciccone, N., & Leonard, H. (June 2012) *A qualitative understanding of factors influencing communication in Rett syndrome.* 7th World Congress on Rett syndrome, New Orleans, Louisiana, USA (Poster presentation)

Urbanowicz, A., Girdler, S., Downs, J., Ciccone, N., & Leonard, H. (June 2012) *A longitudinal analysis of communication abilities in girls and women with Rett syndrome*". 7th World Congress on Rett syndrome, New Orleans, Louisiana, USA (Poster presentation)

Urbanowicz, A., Girdler, S., Ciccone, N., Downs, J., & Leonard, H. (May 2012) *An analysis of communication abilities in girls and women with Rett syndrome.* 12th International Child Neurology Congress, Brisbane, Queensland, Australia (Oral presentation)

Invited oral presentations

Urbanowicz, A. (May & September 2013, April & August 2014, March 2015) *Occupational therapy for individuals with Rett syndrome.* Guest lecture for 4th Year Undergraduate Occupational Therapy Students at Edith Cowan University, Perth, Western Australia

Urbanowicz, A. (May 2014) *Engaging girls and women with Rett syndrome in communication.* Occupational Therapy Australia 2014 Perth Conference, Perth, Western Australia

Urbanowicz, A. (May 2012) *Communication & Rett syndrome.* Australian Rett Syndrome Family Conference, Brisbane, Queensland

Contents

Chapter 1: General introduction 1
1.1 Introduction 1
1.2 Theoretical framework 4
1.3 Communication 6
1.4 Communication abilities in females with Rett syndrome 7
1.4.1 Receiving messages 7
1.4.2 Producing messages 8
1.4.3 Conversation and use of communication devices and techniques 9
1.4.4 Factors influencing performance of communication 10
1.5 Significance of the research 10
1.6 Aim of the research 11
1.7 Thesis outline 12
Chapter 2: Literature review 14
2.1 Introduction 14
2.2 Methods 14
2.2.1 Inclusion and exclusion criteria 14
2.2.2 Search strategy 15
2.2.3 Data extraction and analysis 15
2.3 Results 16
2.3.1 Study description 16
2.3.2 Factors influencing communication abilities 17
2.3.2.1 Body functions and structures 17
2.3.2.2 Activities and participation 19
2.3.2.3 Environmental factors 20
2.3.2.4 Personal factors 24
2.4 Summary 25
Chapter 3: Methodology 37
3.1 Data sources 37

3.1.1 The Australian Rett Syndrome Database (ARSD) 37

3.1.2 International Rett Syndrome Phenotype Database (InterRett) 40

3.2 Case inclusion criteria 40

3.3 Study design 41

3.3.1 Study 1 - Parental perspectives on the communication abilities of their daughters with Rett syndrome 41

3.3.2 Study 2 - Aspects of speech-language abilities are influenced by *MECP2* mutation type in girls with Rett syndrome 43

3.3.3 Study 3 - An exploration of the use of eye gaze and gestures in females with Rett syndrome 44

3.3.4 Study 4 - Choice making in Rett syndrome: A descriptive study using video data 46

Foreword to Chapter 4 51

Chapter 4: Parental perspectives on the communication abilities of their daughters with Rett syndrome 52

4.1 Abstract 52

4.2 Introduction 53

4.3 Methods 55

4.3.1 Procedure 55

4.3.2 Data analysis 56

4.4 Results 56

4.4.1 Expressive communication 58

4.4.1.1 Multimodal communication. 58

4.4.1.2 Expressing discomfort and protesting. 58

4.4.1.3 Making choices. 59

4.4.1.4 Requesting items and activities. 60

4.4.1.5 Requesting attention & socialising. 60

4.4.1.6 Expressing happiness. 61

4.4.2 Receptive communication 61

4.4.2.1 Understanding language. 61

4.4.2.2 Understanding symbols. 63
4.4.2.3 Factors influencing communication 64
4.5 Discussion 64
4.6 Conclusion 69
Foreword to Chapter 5 70
Chapter 5: Aspects of speech-language abilities are influenced by *MECP2* mutation type in girls with Rett syndrome 71
5.1 Abstract 71
5.2 Introduction 72
5.3 Methods 74
5.3.1 Data management 74
5.3.2 Data analysis 75
5.4 Results 75
5.5 Discussion 78
Foreword to Chapter 6 85
Chapter 6: An exploration of the use of eye gaze and gestures in females with Rett syndrome 86
6.1 Abstract 86
6.2 Introduction 87
6.3 Methods 89
6.3.1 Data source 89
6.3.2 Communication variables 90
6.3.3 Other variables 92
6.3.4 Data analysis 93
6.4 Results 93
6.5 Discussion 98
6.6 Conclusions 102
Foreword to Chapter 7 103
Chapter 7: Choice making in Rett syndrome: A descriptive study using video data 104
7.1 Abstract 104

7.2 Introduction 105
7.3 Methods 106
7.3.1 Participants 106
7.3.2 Procedure 107
7.3.2.1 Video coding 107
7.3.2.2 Inter-Rater Reliability 109
7.3.3 Other variables 109
7.3.4 Data analysis 110
7.4 Results 110
7.5 Discussion 115
Chapter 8: Final discussion 119
8.1 Overview 119
8.2 Conclusions 120
8.2.1 Communication abilities vary in girls and women with Rett syndrome 120
8.2.2 Genotype is partly responsible for the variance observed in the use of specific communication modalities 121
8.2.3 Mobility is related to the use of some communication modalities 123
8.2.4 Communication partners play an important role in the success of communicative interactions 124
8.2.5 Both qualitative and quantitative methods are important in the studyof communication abilities in individuals with severe disability 124
8.2.6 The ICF-CY has some limitations in the study of communication in individuals with severe disability 125
8.3 Limitations 126
8.4 Recommendations 127
8.4.1 Recommendations for future research 127
8.4.2 Recommendations for clinical practice 129
8.4.3 Recommendations for caregivers 130
8.5 Knowledge translation 130
8.6 Final comments 131

References 132

Appendix A: Literature review data extraction form 151

Appendix B: Participant information sheet and consent form 152

Appendix C: Interview guide 155

Appendix D: Edith Cowan University Human Research Ethics Approval 156

Appendix E: Princess Margaret Hospital for Children Human Research Ethics Approval for the ARSD 157

Appendix F: Princess Margaret Hospital for Children Human Research Ethics Approval for InterRett 160

Appendix G: Example completed video coding framework 163

List of tables

Table 1. Summary of reviewed articles evaluating the relationship between communication abilities and factors in females with Rett syndrome (n=38). 27
Table 2. Summary of the methodology of each study including their objectives, design, data source and relevant ICF-CY chapters. 49
Table 3. Characteristics of the girls and women with Rett syndrome (n=16). 57
Table 4. Body functions and structures, and activities influencing communication abilities..... 65
Table 5. Contextual factors influencing communication abilities. 66
Table 6. Likelihood of experiencing a regression in speech-language abilities by type of mutation (n=766). 77
Table 7. Likelihood of speech-language abilities before and after experiencing a speech-language regression by type of *MECP2* mutation. 79
Table 8. The level of speech-language abilities of girls who did not experience a speech-language regression by type of mutation (n=185). 80
Table 9. Eye gaze and gestures scores according to age group and *MECP2* mutation type (n=151). 96
Table 10. Eye gaze and gestures scores according to gross motor abilities, adjusted for age and *MECP2* mutation type (n=117). 97
Table 11. The ability to request help or an object, and attention according to eye gaze and gestures scores. 97
Table 12. Proportion of *MECP2* mutation types and walking trajectories of our sample (n=64) and those in the ARSD not included in this study (n=236). 111
Table 13. Proportion able to make a choice by sample characteristics. 112
Table 14. The frequency of different communication modalities girls and women with Rett syndrome used to make a choice. 115

List of figures

Figure 1. Schemic diagram of the ARSD showing recruitment, longitudinal data collection from multiple sources, and multivariate analyses of outcomes. 39
Figure 2. Social interactions between the girls and women with Rett syndrome and their communication partners. 62
Figure 3. Flow chart describing the speech-language abilities and regression in speech-language abilities in our sample (n=766). 76
Figure 4. Adjusted mean age of regression of speech-language abilities (months) by type of mutation with 95% confidence intervals (n=495). 77
Figure 5.Eye gaze scores for individuals according to their age (n=151). 95
Figure 6. Gestures scores for individuals according to their age (n=151). 95
Figure 7. Flowchart of the selection of videos for inclusion. 108
Figure 8. Kaplan-Meier survival curve for the ability to make a choice by time (n=53). 114
Figure 9. Kaplan-Meier survival curve for the ability to make a choice at different ages, by time (n=53). 114

List of abbreviations

AAC	Augmentative and alternative communication
ARSD	Australian Rett Syndrome Database
CI	Confidence Interval
CSBS DP ITC	Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist
EEG	Electroencephalography
FAC	Functional Ability Checklist
ICF	International Classification of Functioning, Disability and Health
ICF-CY	International Classification of Functioning, Disability and Health - Child & Youth Version
InterRett	International Rett Syndrome Phenotype Database
IPCA	Inventory of Potential Communicative Acts
MECP2	*Methyl-CpG Binding Protein 2*
RRR	Relative Risk Ratio
OR	Odds Ratio
PECS	Picture Exchange Communication System
SD	Standard Deviation
SLP	Speech-language Pathologist
VOCA	Vocal Output Communication Aid
WeeFIM	Functional Independence Measure (Paediatric Version)

Chapter 1: General introduction

1.1 Introduction

"A voice gives people control. It gives people the opportunity to learn about themselves and express who they are. It gives people the opportunity to express their needs, wants, preferences and opinions. Inevitably, having a voice improves our quality of life. It allows us to become who we are and achieve our potential. As a result, we are happier, more content, more understood, we suffer less anxiety and can lead healthier lifestyles. If you were to be locked in your body, your voice box removed and had no way to communicate, how do you think you would feel?" –
Janie Beaumont, mum to Olive who has Rett syndrome

As highlighted in the quote above, being able to communicate is central to leading a meaningful, functional and independent life. People with severe intellectual and physical impairments often experience challenges with communicating and require extensive support to participate in everyday life (Duker, van Driel, & van de Bercken, 2002; Parkes, Hill, Platt, & Donnelly, 2010). Frequently these individuals rely on communication methods that are nonsymbolic, (Didden et al., 2010; McLean, Brady, McLean, & Behrens, 1999) and preintentional (Iacono, Carter, & Hook, 1998; McLean et al., 1999) such as vocalisations, body movements and facial expressions (Didden et al., 2009; Stephenson & Dowrick, 2005). Communication partners are required to interpret these behaviours and assign meaning to them. Due to the difficulty of interpreting such behaviours, people with severe physical and intellectual disability are often misunderstood (Maes, Vos, & Penne, 2010), particularly if the communication partner is not familiar with the individual (Bartolotta, Zipp, Simpkins, & Glazewski, 2011). This can have a negative impact on the person's ability to participate in everyday activities (Markham, van Laar, Gibbard, & Dean, 2009; McCormack, McLeod, Harrison, & McAllister, 2010), their quality of life (Hostyn & Maes, 2009) and wellbeing (Hickson et al., 2008).

Rett syndrome is a neurodevelopmental disorder generally associated with severe language, physical and intellectual impairments, each of which contributes to difficulties with communication (Bartolotta et al., 2011; Didden et al., 2010). About one in 9000 girls is affected (Fehr, Bebbington, Nassar, et al., 2011)[1]. The syndrome was first described in 1966 by Dr Andreas Rett (cited in Hagberg, Aicardi, Dias, & Ramos, 1983) but it did not become widely known in the medical and research community until Bengt Hagberg with his colleagues

[1] As Rett syndrome almost exclusively occurs in females, individuals with Rett syndrome will be referred to as females, girls and/or women, whichever is most appropriate, in this thesis.

published a case series of 35 females in the English language literature (Hagberg et al., 1983). The first diagnostic criteria for Rett syndrome were developed in 1985 (Hagberg, Goutières, Hanefeld, Rett, & Wilson, 1985). The diagnostic criteria have since been revised a number of times with the latest published in 2010 (Hagberg, Hanefeld, Percy, & Skjeldal, 2002; Neul et al., 2010; The Rett Syndrome Diagnostic Criteria Working Group, 1988).

Most girls with Rett syndrome have a largely typical period of development in the first six to 12 months of life. After this time, a period of regression is experienced where previously achieved abilities, including expressive communication, diminish or are lost. Other diagnostic features include the development of hand stereotypies such as wringing, clapping or rubbing and impaired motor function (Neul et al., 2010). Comorbidities such as seizures (Bao, Downs, Wong, Williams, & Leonard, 2013) and scoliosis (Downs, Torode, et al., 2016) often develop with age. The level of cognitive impairment associated with Rett syndrome is likely to be severe but is rarely formally assessed because of the unique language and physical impairments of Rett syndrome which prohibit the use of conventional cognitive assessments (Berger-Sweeney, 2011; Byiers & Symons, 2012). The overall clinical severity of the syndrome varies between females, with some experiencing a less severe and others experiencing a more severe phenotype (Bebbington et al., 2008; Cuddapah et al., 2014). Internationally the life expectancy of those with Rett syndrome has been difficult to document due to a lack of population-based data with a long follow-up time period. However, in Australia survival rates for girls and women with Rett syndrome in 2014 were 77.6% at 20 years of age, 71.5% at 25 years of age and 59.8% at 37 years of age (Anderson, Wong, Jacoby, Downs, & Leonard, 2014).

The primary cause of Rett syndrome is a mutation in the *methyl-CpG-binding protein 2 (MECP2)* gene located on the X chromosome and as a result the syndrome is seen almost exclusively in females (Amir et al., 1999). This gene is responsible for producing the MeCP2 protein, a neuronal chromatin structure (Skene et al., 2010) important to the development and maintenance of the brain and nervous system (Cohen et al., 2011). The discovery of the causal link between *MECP2* mutations and Rett syndrome allowed clinical diagnosis to be confirmed with genetic testing. More than 400 different *MECP2* mutations have been identified as causing Rett syndrome (Christodoulou, Grimm, Maher, & Bennetts, 2003). Of these, the eight most frequently reported point mutations are p.Arg106Trp, p.Arg133Cys, p.Arg168*, p.Arg255*, p.Arg270*, p.Arg294*, p.Arg306Cys and p.Thr158Met. Other commonly reported *MECP2* mutations in Rett syndrome include early truncations, C-terminal deletions and large deletions (Christodoulou et al., 2003).

There is consensus that *MECP2* mutation type influences the clinical presentation of Rett syndrome with some mutations generally associated with a less severe and others with a more severe presentation. For example, females with a p.Arg294* mutation have been reported to have a mild phenotype and experience a delayed onset of regression (Bebbington et al., 2008) and hand stereotypies (Bebbington et al., 2008; Cuddapah et al., 2014), to be more likely to have voluntary hand use (Colvin et al., 2004; Cuddapah et al., 2014) and to have learnt to walk (Bebbington et al., 2008; Colvin et al., 2004; Cuddapah et al., 2014). Those with a p.Arg133Cys mutation have also been reported to have a mild phenotype associated with a delayed onset of regression and hand stereotypies, an increased likelihood of single word and phrase use, and of having walked at some point in time (Bebbington et al., 2008; Cuddapah et al., 2014). In contrast, individuals with a p.Arg270* mutation are more likely to have a severe phenotype and experience feeding difficulties (Bebbington et al., 2008), and an earlier onset of loss of social interaction (Colvin et al., 2004) and hand stereotypies (Colvin et al., 2004; Cuddapah et al., 2014). Similarly, individuals with a p.Arg168* mutation have been reported to experience a severe phenotype type with severe feeding difficulties (Bebbington et al., 2008), an earlier onset of loss of social interaction (Colvin et al., 2004) and a decreased likelihood of walking and retaining hand use (Cuddapah et al., 2014; Neul et al., 2008). Females with a large deletion appear to be more severely affected when compared to girls and women with other mutations as a collective group, particularly in terms of walking ability and presence of epilepsy (Bebbington et al., 2012).

Over the years several atypical subtypes or variants of Rett syndrome have been suggested including the preserved speech, early seizure and the congential variants (Hagberg & Skjedal, 1994; Neul et al., 2010; Zappella, Gillberg, & Ehlers, 1998). According to the latest diagnostic criteria for Rett syndrome (Neul et al., 2010), the preserved speech variant is characterised by a mild phenotype and the ability to say single words or phrases and is often associated with *MECP2* mutations such as p.Arg133Cys (Kerr, Archer, Evans, Prescott, & Gibbon, 2006; Leonard et al., 2003) and C-terminal deletions (Kerr et al., 2006). The early seizure variant is characterised by early onset of seizures, usually by five months of age, and the congential variant is characterised by atypical early development and regression usually within the first five months of life. However, unlike the preserved speech variant, *MECP2* mutations are very rarely associated with these other variants (Neul et al., 2010) which likely represent different disorders to Rett syndrome (Fehr et al., 2013; Kortüm et al., 2011). Overall Rett syndrome, with its associated features and comorbidities, has a significant and severe impact on the communicative ability of affected girls and women.

1.2 Theoretical framework

The International Classification of Functioning, Disability and Health (ICF) is a framework that describes health and health-related domains using standard language and definitions (World Health Organization., 2001). It integrates the medical and social models of health and proposes that disability occurs as an interaction of health characteristics and contextual factors (World Health Organization., 2001). The ICF was designed to meet the needs of various disciplines and different sectors with specific aims including: to provide a scientific basis for understanding and studying health and health-related states, outcomes and determinants and to establish a common language for describing health and health-related states in order to improve communication between different users, such as health-care workers, researchers, policy-makers and the public, including people with disabilities (World Health Organization., 2001).

The ICF framework is composed of four domains:

1. **Body Functions and Structures.** This domain describes the physiological functions and the parts of an individual's body. Examples include mental, neuromusculoskeletal and movement-related functions, and structures of the nervous system and those related to movement. Significant deficits or abnormalities of body function or structure are defined as impairments.
2. **Activities and Participation.** Activities are the tasks performed by an individual and include communication, learning and applying knowledge, and mobility. Difficulties in the execution of activities are referred to as activity limitations. Participation describes an individual's engagement in a life situation and difficulties in participation are referred to as participation restrictions. The acitivities and participation domain is qualified by the two qualifiers: performance and capacity. The performance qualifier describes what an individual does in his or her current environment whereas the capacity qualifier describes an individual's highest probable level of functioning in a standardised or uniform environment.
3. **Environmental Factors.** This domain describes the physical, social and attitudinal environments surrounding an individual such as products, technology, attitudes, support and relationships. Environmental factors interact with components of Body Functions and Structures and Activities and Participation. They may be classified as either barriers or facilitators to functioning.
4. **Personal Factors.** This domain refers to those features of an individual, such as age, gender and lifestyle, which are not directly a part of a health condition but which may impact on them.

These four domains are classified under the umbrella terms functioning (body functions, activities and participation) and disability (impairments, activity limitations and participation restrictions), and contextual factors (environmental and personal factors). An individual's level of functioning in a specific domain is an interaction between the health condition and contextual factors (World Health Organization., 2001). The interactions between these domains are dynamic and therefore interventions in one domain have the potential to modify one or more other domains.

The ICF has numerous applications including use as a statistical (e.g. collecting and recording data) and research tool (e.g. the development of core sets of items relevant the management of specific conditions such as autism) (Bölte et al., 2014), as a framework for literature reviews (Foley, Dyke, Girdler, Bourke, & Leonard, 2012; O'Halloran & Larkins, 2008) and as a clinical tool (e.g. facilitating client-centred care (Atkinson & Nixon-Cave, 2011). Specifically in relation to communication, the ICF (World Health Organization., 2001) has provided a framework to help define and explore communication in people with disability (Howe, 2008; Simeonsson, Bjorck-Akesson, & Lollar, 2012). The ICF has been recommended as a conceptual framework for exploring communication both in research and clinical contexts (McLeod & McCormack, 2007; Simeonsson, 2003). Specific applications of the ICF in these contexts include measuring levels of impairment (McLeod & Threats, 2008; Simeonsson, 2003) and the assessment of communication disabilities (McLeod & Threats, 2008), the provision of a uniform language for the classification of communication disabilities (Simeonsson, 2003), describing augmentative and alternative communication (Raghavendra, 2007) and comparing the prevalence of speech, hearing and communication disabilities among samples (Mulhorn & Threats, 2008). In addition the ICF has been validated as a reliable tool for describing the functional profile, including the severity of communication limitations, and the multiple factors influencing health conditions in children and adolescents with disabilities such as cerebral palsy, autism and non-specific learning disabilities (Battaglia, 2004). A recommendation of the first World Report on Disability (World Health Organization & The World Bank, 2011) was for all researchers to adopt the ICF (World Health Organization., 2001) to collect disability data worldwide.

In 2007 the World Health Organization published the International Classification of Functioning, Disability and Health - Children & Youth Version (ICF-CY). The ICF-CY is derived from the ICF (World Health Organization, 2007) and includes additional content to encompass the body functions and structures, activities, participation and environments specific to infants, toddlers, children and adolescents (World Health Organization, 2007). The ICF-CY (World Health Organization, 2007) was used in this thesis to provide an overall framework for

describing and understanding the performance of communication, as an activity, in girls and women with Rett syndrome. The ICF-CY (World Health Organization, 2007) provides operational definitions of the health and health-related domains that were used to describe communication and the body functions and structures, activities and participation, environmental factors and personal factors that may influence communication performance in girls and women with Rett syndrome. As described earlier in this chapter many girls and women with Rett syndrome experience varied and often severe impairments that can limit their ability to perform a range of activities, including communication. However environmental factors, such as assistive products and technology for communication, and personal factors such as age, may also impact the performance of communication. Therefore, the ICF-CY (World Health Organization, 2007) was used in the research to provide a framework that would allow for the holistic study of communication in females with Rett syndrome.

1.3 Communication

Communication is classified under the Activities and Participation domain of the ICF-CY and can be described as the activity of exchanging messages between two or more people (World Health Organization, 2007). Messages may verbal, written or sign language, body gestures, or photos, pictures, signs or symbols (World Health Organization, 2007). According to the ICF-CY (World Health Organization, 2007), communication involves the tasks of receiving and producing communication messages, conversation and use of communication devices and techniques. Additionally, communication may also involve many other activities classified in other domains of the ICF-CY including those classified in the "Learning and applying knowledge" domain such as "reading", "writing" and "solving problems" which includes making decisions (O'Halloran & Larkins, 2008).

As outlined above, the ICF-CY (World Health Organization, 2007) provides a framework and language to describe the components of communication including communication modalities (e.g. verbal, written) and communicative functions (e.g. producing messages, conversation). However, the Communication chapter the ICF-CY (World Health Organization, 2007) does not clearly identify the full range of communication modalities an individual with severe disability may use (e.g. eye gaze) or the functions they may communicate (e.g. requesting). For this reason an additional tool, The Communication Matrix (Rowland, 2004), was used in combination with the ICF-CY (World Health Organization, 2007) to describe the communication modalities and communicative functions of girls and women with Rett syndrome within this research.

The Communication Matrix (Rowland, 2004) is an instrument designed to evaluate the expressive communication skills of children with severe and multiple disabilities (Rowland, 2011). The Matrix (Rowland, 2004) was designed to pinpoint how an individual is communicating using multiple modalities and to provide a framework for determining logical communication goals. The instrument can accommodate any type of communication modality and therefore describes these in more detail than the ICF-CY (World Health Organization, 2007). The Communication Matrix (Rowland, 2004) can be completed online and in October 2010, over 12,500 Matrix profiles on over 12,000 individuals had been completed (Rowland & Fried-Oken, 2010). This shows the Communication Matrix (Rowland, 2004) is widely used. Also the Communication Matrix (Rowland, 2004) has been previously used in research to assess communication abilities in children with multiple disabilities and visual impairments or deaf-blindness (Pizzo & Bruce, 2010), children with a variety of diagnoses including autism, developmental delay and intellectual disability (Rowland, 2011) and an adult with multiple disabilities (Cascella, 2014).

Following is a discussion of how females with Rett syndrome perform the communication tasks outlined by the ICF-CY (World Health Organization, 2007); receiving messages, producing messages and conversation and use of communication devices and techniques, incorporating the language and definitons of ICF-CY (World Health Organization, 2007) and added detail from the Communication Matrix (Rowland, 2004).

1.4 Communication abilities in females with Rett syndrome

1.4.1 Receiving messages

Receiving messages involves the comprehension of the meanings of spoken messages, and messages conveyed by gestures, symbols and drawings, formal sign language and written language (World Health Organization, 2007). The level of cognitive functioning in females with Rett syndrome is rarely formally assessed as the severe language and motor impairments of Rett syndrome prohibit the use of conventional cognitive assessments (Byiers, Dimian, & Symons, 2014). Likewise, it is currently difficult to accurately measure the receptive communication abilities of girls and women with Rett syndrome. A few studies have attempted to measure the abilities of a small number of girls and women to respond to verbal instructions using eye gaze technology (Baptista, Mercadante, Macedo, & Schwartzman, 2006; Velloso, Araυjo, & Schwartzman, 2009) and to match spoken words to symbols presented on a

computer screen demonstrating variability in these abilities abilities among females with Rett syndrome (Hetzroni, Rubin, & Konkol, 2002). Using the Vineland Adaptive Behavior Scale (Sparrow, Balla, & Cicchetti, 1984), Dahlgren Sandberg, Ehlers, Hagberg and Gillberg (2000) found that females with Rett syndrome (n=8) had limitations in their receptive abilities although their ability to receive messages may still be greater than their ability to produce messages. In a larger online survey (n=141), the majority of respondents (parent, teacher or SLP) were undecided or unsure as to whether the female they cared for could read one or more single words, although 73% of respondents strongly agreed that the female could understand at least 10 spoken words (Bartolotta et al., 2011). Additionally, a functional assessment of communication in one girl indicated that the she responded to gestures and environmental cues in the classroom, such as copying the other children, rather than verbal instruction (Brady & Halle, 1997). Retrospective analysis of family videos of 15 girls prior to their diagnosis of Rett syndrome found girls responded to their name when called less than expected (Townend, Bartl-Pokorny, et al., 2015). These findings suggest that females with Rett syndrome have difficulties with receiving messages although they may have a greater ability to receive spoken messages as opposed to written messages, and gestures and other environmental cues that often accompany verbal instructions may be associated with this greater ability. However, all but one study included 15 or less participants and the one study with a large sample was restricted only to those who had access to the internet. Therefore further investigation into the receptive abilities of females with Rett syndrome is warranted.

1.4.2 Producing messages

Producing messages involves speaking, singing, pre-talking, and producing nonverbal messages such as body gestures, signs, symbols, drawings and photographs (World Health Organization, 2007). Retrospective analysis of family videos of small numbers of young girls prior to their diagnosis suggests that the ability to produce communication message may develop atypically from an early age (Bartl-Pokorny et al., 2013; Marschik, Bartl-Pokorny, et al., 2014; Marschik, Sigafoos, et al., 2012). A study comparing two girls with Rett syndrome with a typically developing girl between the ages of nine and 24 months showed that the two girls with Rett syndrome used less communication modalities in comparison to the typically developing girl (Marschik, Bartl-Pokorny, et al., 2014). In other studies, girls with Rett syndrome were also found to vary in their ability to produce vocalisations, with some failing to acquire babbling by 24 months of age (Marschik, Pini, et al., 2012) and to use gestures (Marschik, Sigafoos, et al., 2012). Video observations also revealed that girls with Rett syndrome varied in the functions they communicated (Bartl-Pokorny et al., 2013; Marschik, Kaufmann, et al., 2012).

Current evidence suggests that after regression few girls and women use speech to communicate and most rely on eye gaze, a nonverbal form of communication, to express their needs, wants, preferences and opinions (Bartolotta et al., 2011; Cass et al., 2003; Cianfaglione et al., 2015; Didden et al., 2010). Other reported nonverbal forms of communication used by females with Rett syndrome include body movements (Bartolotta et al., 2011; Didden et al., 2010; Hetzroni & Rubin, 2006) and less frequently gestures (Bartolotta et al., 2011; Brady & Halle, 1997), signs (Bartolotta et al., 2011; Kerr et al., 2006) and communication devices (Bartolotta et al., 2011). Pre-talking behaviours such as vocalisations, laughing or smiling (Didden et al., 2010; Hetzroni & Rubin, 2006), and crying or screaming (Brady & Halle, 1997; Didden et al., 2010) have also been described as communicative among this population. Females may use these forms of communication to serve a number of functions including choice making (Cass et al., 2003; Cianfaglione et al., 2015; Didden et al., 2010), requesting, social convention (e.g. greeting), bringing attention to themselves, and to reject, comment and answer (Didden et al., 2010). Some parents and professionals believe a small proportion of girls and women with Rett syndrome do not use any type of communication system (Bartolotta et al., 2011). Most of this literature had small sample sizes and the criteria used to verify diagnosis of Rett syndrome in the participants varied greatly, limiting the generalisability of the findings. Therefore based on the current literature it is difficult to draw conclusions and further research is required to confirm what communicative forms are used to serve different communicative functions.

1.4.3 Conversation and use of communication devices and techniques

According to the ICF-CY (World Health Organization, 2007), conversation is exchanging thoughts and ideas between two or more people and the use of communication devices and techniques refers to using devices, techniques or other means for the purposes of communicating such as calling a friend on a telephone and using computers as a means of communication (World Health Organization, 2007). Communication devices and techniques do not include assistive products and technology for communication (e.g. communication boards) which are considered an environmental factor according to the ICF-CY and are included in the "Products and technology" chapter (World Health Organization, 2007).

Very few studies have described conversation between females with Rett syndrome and others and none have described the use of communication devices and techniques such as telephones. Kerr and colleagues (2006) investigated communication skills in 13 females who

could converse through speech or signing, who were 10 years of age or older and had an identified *MECP2* mutation. Reportedly 11/13 of the females had some conversational speech that was appropriate to the context (Kerr et al., 2006). More recently in 2014, Marschik and colleagues described the development of speech-language and communication functions in a case study of a female with Rett syndrome. They found the female able to give and understand feedback, to reply appropriately to yes/no and wh- questions but experienced difficulties with dialogue. Often she initiated conversation but was unable to keep up the topic for a longer period of time, even with a cooperative communication partner. Largely her conversations consisted of answers and short sentences that relation to the context was not always clear. The paucity of research on conversation among females with Rett syndrome highlights the need for research into this area.

1.4.4 Factors influencing performance of communication

As outlined above, the ability to receive and produce messages and to converse appears to vary between with females with Rett syndrome. There are a number of potential reasons for this variance including personal characteristics such as age (Didden et al., 2010; Halbach et al., 2008; Halbach et al., 2013), *MECP2* mutation type (Bebbington et al., 2008; Cuddapah et al., 2014; Neul et al., 2008), functional abilities such as hand function(Cass et al., 2003) and the presence of dyspraxia (Bartolotta et al., 2011; Woodyatt & Ozanne, 1994) or epilepsy (Didden et al., 2010). Environmental factors may also help explain some of the variation observed in communication abilities including place of residence (Didden et al., 2010), characteristics of the communication partner (Bartolotta & Remshifski, 2013) and the use of communication interventions (Sigafoos et al., 2009; Stasolla et al., 2015). However there is a lack of consensus between these studies and the majority were conducted with small sample sizes thus limiting the generalisability of the findings. Therefore the impairments in body function and structure, activity limitations and participation restrictions, and environmental and personal factors that influence the performance of communication in Rett syndrome remain largely unknown.

1.5 Significance of the research

As outlined in the previous section, the current evidence-base for communication in Rett syndrome is limited. Limitations include few studies describing the ability to receive messages and to converse and use communication devices and techniques, low quality evidence describing the ability to produce messages and mixed findings regarding the factors influencing the performance of communication. As a result, there is little high quality evidence available to

guide the practice of professionals such as speech-language pathologists, occupational therapists, educators and medical doctors. Clearly, there is a need to further investigate the performance of communication of girls and women with Rett syndrome to build on and strengthen the current evidence-base.

For professionals this research will contribute new knowledge about specific communication tasks and the varied factors that influence performance of these tasks to their evidence base. This is vital for when they are counselling families and caregivers, particularly around the time of diagnosis when families and caregivers are first learning about Rett syndrome and figuring out the diagnosis means for their future lives. Furthermore having an accurate knowledge of the communication abilities of girls and women with Rett syndrome and how impairments, activity limitations and contextual factors impact performance is central to being able to provide appropriate and effective communication and education interventions.

For families and caregivers this thesis will provide new information about the communication abilities of the girls and women for whom they care and the numerous factors that need to be taken into consideration when communicating with them. This is particularly important as often family members and caregivers are the girl's/woman's main communication partner. Therefore they are largely responsible for shaping communication interactions and informing other communication partners of how to communicate with the girl or woman. The findings of this thesis will also empower families and caregivers to better advocate for the communication rights of girls and women with Rett syndrome. This is central to ensuring individuals with severe disabilities can participate in everyday life and experience the best quality of life possible (United Nations Economic and Social Commission for Asia and the Pacific, 2012).

1.6 Aim of the research

The overall aim of this thesis was to describe the performance of communication tasks in girls and women with Rett syndrome and to investigate factors that are positively and negatively associated with performance.

Research objectives:

(1) Describe communication tasks including:

- how girls and women communicate in everyday life according to parents;
- the level of speech-language abilities before and after language regression;
- the use of eye gaze and gestures for requesting; and,

- the ability to make choices.

(2) Describe relationships between a range of factors and communication performance including:

- factors that parents believe are barriers or facilitators to successful communication;
- relationships between speech-language abilities and genotype; and,
- relationships between genotype, age and motor abilities and the use of eye gaze and gestures;
- relationships between genotype, age, the ability to walk and grasp, and speech language abilities and the ability to make choices.

1.7 Thesis outline

This thesis includes eight chapters:

- Chapter One: Introduction

This chapter provides a brief background to the significance and purpose of the research and also includes an overview of the thesis.

- Chapter Two: Literature review

Chapter two evaluates the literature on relationships between communication abilities and different factors, such as *MECP2* mutation type, in girls and women with Rett syndrome using the International Classification of Functioning, Disability and Health - Child and Youth Version (ICF-CY) as a framework (World Health Organization, 2007).

- Chapter Three: Methodology

Chapter three provides background information about the mixed methods employed in this research and the two databases, the Australian Rett Syndrome Database (ARSD) and the International Rett Syndrome Phenotype Database (InterRett), which provided data and participants for this research.

- Chapter Four: Parental perspectives on the communication abilities of their daughters with Rett syndrome

This qualitative study addresses two research questions from the perspective of parents (1) how do females with Rett syndrome communicate in everyday life? and (2) what factors act as

barriers or facilitators to successful communication? Results from 16 interviews with parents are presented under the domains of the ICF-CY (World Health Organization, 2007).

- Chapter Five: Aspects of speech-language abilities are influenced by *MECP2* mutation type in girls with Rett syndrome

This study describes the speech-language abilities of girls aged 15 years or younger and investigates relationships with genotype. Caregiver questionnaire data from the ARSD and InterRett were used (n=766).

- Chapter Six: An exploration of the use of eye gaze and gestures in females with Rett syndrome

The study described in Chapter six uses caregiver questionnaire data (n=151) from the ARSD to investigate the relationships between the use of eye gaze and gestures, and making requests, and understand how genotype, gross motor abilities and age influence these skills in girls and women with Rett syndrome.

- Chapter Seven: Choice making in Rett syndrome: A descriptive study using video data

Chapter seven describes the choice making abilities of girls and women and relationships with age, *MECP2* mutation type and functional abilities. This study uses video data provided to the ARSD by parents/caregivers of girls and women with Rett syndrome engaging in choice making interactions with familiar communication partners (n=64).

- Chapter Eight: Final discussion

The final chapter discusses and brings together the findings and conclusions from each of the studies included in this thesis and outlines the directions for future research.

Chapter 2: Literature review

2.1 Introduction

Communication is an important everyday activity that allows individuals to engage with others and participate in society. As described in the previous chapter, females with Rett syndrome often experience severe difficulties with both producing and receiving communication messages (Bartolotta et al., 2011; Dahlgren Sandberg et al., 2000). However the level of difficulty experienced appears to vary between females. For example, a small proportion of females have been described to use words to communicate while the majority have been described to use non-verbal forms of communication such as eye gaze and body movements (Bartolotta et al., 2011; Didden et al., 2010). These observed variations in the performance of communication tasks may be due to differences in motor and cognitive functions between the females (Rowland & Fried-Oken, 2010), and also contextual factors such as the attitudes and knowledge of communication partners (Shokoohi-Yekta & Hendrickson, 2010). An understanding of the barriers and facilitators to successful communication in females with Rett syndrome is required to make an accurate assessment of communication abilities and prescribe appropriate interventions and strategies.

Chapter 1 of this thesis reviewed literature on the performance of communicative tasks by females with Rett syndrome and provided an outline of the various factors that may influence the performance of communication tasks. This chapter provides further detail on the factors (e.g. *MECP2* mutation type) that may act as facilitators and barriers to the performance of various communication tasks, such as speaking. The ICF-CY (World Health Organization, 2007) was used as a conceptual framework for this literature review chapter to allow for the consideration of multiple factors and interactions between factors that result in a particular level of functioning and performance of an activity (i.e. communication).

2.2 Methods

2.2.1 Inclusion and exclusion criteria

Literature satisfying the following inclusion criteria was included in this review: (1) the study exclusively included female participant/s with a diagnosis of Rett syndrome; (2) the article was published in the English language in a peer-reviewed journal between the years of 2000 - 2015; and (3) relationships between at least one factor (e.g. age) and a communication outcome (e.g. ability to say words) were described or analysed. Literature reviews were excluded but studies

of all other levels of evidence were suitable for inclusion including both quantitative and qualitative articles (Merlin, Weston, & Tooher, 2009). Studies were restricted to those published since the year 2000 as the link between mutations in the *MECP2* gene and Rett syndrome was identified in 1999 (Amir et al., 1999) and therefore studies prior to this time would not have considered the type of *MECP2* mutation as a possible factor influencing communication abilities. Published work resulting from this thesis was not included in the review.

2.2.2 Search strategy

An electronic search of the following databases was conducted: Cumulative Index for Allied Health Literature (CINAHL) (2000 - 2015), Educational Resources in Education Clearinghouse (ERIC) (2000 - 2015), MEDLINE (2000 - 2015) and PsycINFO (2000 - 2015). Two categories of terms were used in the search; participant keywords (*Rett syndrome OR Retts disorder*) and communication keywords *(communication OR speech OR language OR gesture*)*. The titles and abstracts of search results were screened for inclusion prior to the retrieval of the full text article. Retrieved full text articles were further assessed against the inclusion criteria and the reference lists of those meeting the criteria were manually searched to identify additional articles for inclusion.

2.2.3 Data extraction and analysis

Data was extracted from included studies to develop a summary of each article outlining the following components: (1) participants, (2) study design and level of evidence, (3) communication assessment and/or intervention, (4) methods of data analysis, (5) main findings in relation to factor/s influencing communication abilities, and (6) the strengths and limitations of each study (Appendix A). The National Health and Medical Research Council (NHMRC) guidelines (Merlin et al., 2009) were used to classify the design and level of evidence of included studies, with the exception of case studies that are not assigned a level of evidence in this classification. A narrative approach was adopted to analyse and synthesise the findings of included articles according to the components of the ICF-CY (World Health Organization, 2007).

2.3 Results

2.3.1 Study description

All 38 studies included in this review were of level IV evidence or a case study (Merlin et al., 2009). A variety of study designs were used with 15 cross-sectional studies, 11 case series with a pre-test/post-test, eight case series without a pre-test or post-test and four case studies. The number of participants in each study ranged from one to 974. Although a total of 3,128 individuals with Rett syndrome were reported on across the studies, this number may include the same individual in multiple studies. Methods used to collect and analyse data varied greatly across the studies with most using caregiver questionnaire or interview data, or direct or video observations. In terms of the age of the participants, some studies reported on the frequency of the age groups, some reported mean and standard deviation or range data, and others used a combination of these methods. Therefore it is difficult to provide the collective age range of participants across all studies. The method by which a diagnosis of Rett syndrome was confirmed differed across the studies and included the use of diagnostic criteria (Cass et al., 2003; Chae, Hwang, Hwang, Cheong, & Kim, 2004; De Bona et al., 2000; Elefant & Wigram, 2005; Fabio, Giannatiempo, Antonietti, & Budden, 2009; Fabio, Giannatiempo, Oliva, & Murdaca, 2011; Neul et al., 2008; Neul et al., 2014; Weaving et al., 2003; Yamashita et al., 2001), by a medical professional or institution (Halbach et al., 2008; Halbach et al., 2013; Hetzroni & Rubin, 2006; Hetzroni et al., 2002; Ryan et al., 2004), a stated diagnosis in the presence of a positive *MECP2* mutation (Huppke, Held, Hanefeld, Engel, & Laccone, 2002; Marschik, Bartl-Pokorny, et al., 2014; Vignoli et al., 2010), by caregiver/questionnaire respondent report (Bartolotta & Remshifski, 2013; Bartolotta et al., 2011; Didden et al., 2010; Wandin, Lindberg, & Sonnander, 2015) or a combination of these methods (Bebbington et al., 2008; Bebbington et al., 2012; Leonard et al., 2003; Marschik, Vollmann, et al., 2014; Townend, Bartl-Pokorny, et al., 2015). Several studies did not clearly describe how Rett syndrome diagnosis was confirmed and included statements such as “participants had a clinical diagnosis of classic Rett syndrome” (Byiers et al., 2014; Elefant & Lotan, 2004; Fabio, Castelli, Marchetti, & Antonietti, 2013; Koppenhaver, Erickson, Harris, et al., 2001; Koppenhaver, Erickson, & Skotko, 2001; Nielsen, Ravn, & Schwartz, 2001; Sigafoos, Woodyatt, Tucker, Roberts-Pennell, & Pittendreigh, 2000; Skotko, Koppenhaver, & Erickson, 2004; Stasolla et al., 2014; Stasolla et al., 2015; Velloso et al., 2009; Yasuhara & Sugiyama, 2001). The characteristics of each study included in this review are summarised in Table 1.

2.3.2 Factors influencing communication abilities

The majority of studies (66%, 25/38) investigated the impact of only one factor, such as genotype or an intervention, on a communication outcome.

2.3.2.1 Body functions and structures

Although females with Rett syndrome often experience a range of severe impairments in this domain of the ICF-CY (World Health Organization, 2007), only some have been studied in relation to communication abilities. These impairments include *MECP2* mutation type, motor abilities, and epilepsy. The relationship between genotype and the ability to speak was investigated in eight studies (Bebbington et al., 2008; Bebbington et al., 2012; Chae et al., 2004; Huppke et al., 2002; Leonard et al., 2003; Neul et al., 2008; Weaving et al., 2003). Of these studies one also investigated the relationship between genotype and nonverbal communication (Weaving et al., 2003) and another also assessed the relationship between genotype and nonverbal and receptive communication (Neul et al., 2014).

Early studies examining relationships between genotype and aspects of phenotype were often limited by small sample sizes. An international study published in 2003 found the presence of a mutation, in comparison to no detected mutation, was associated with poorer language abilities ($p=0.038$, $n=74$) with no identified relationship with nonverbal communication (Weaving et al., 2003). Later in 2004, Chae and colleagues reported that cases with nonsense mutations tended to show more severe language impairments (66.7%, 10/15) but the proportion of severe language impairment in other mutation groups was neither described nor compared statistically. A larger study found the ability to speak in 123 females did not vary according to type of *MECP2* mutation, using the categories of truncating, missense or deletion, nor the location of the mutation (NLS or TRD region) (Huppke et al., 2002). Due to the heterogeneity of *MECP2* mutation classification systems used in the above studies and relatively small sample sizes it is difficult to draw meaningful conclusions in regards to the relationships between *MECP2* mutation type and communication abilities based on the studies outlined above.

Well-powered international (Bebbington et al., 2008; Leonard et al., 2003) and US (Neul et al., 2008) studies found that generally females with a p.Arg133Cys mutation had better language abilities in comparison to those with other mutations. Those with a p.Arg270*, p.Arg255* (Bebbington et al., 2008) or p.Arg168* (Neul et al., 2008) mutation were the least likely to be

able to speak. The same data source as used in the international studies, InterRett, was also used to compare the phenotype of large deletions with that of all other mutations (Bebbington et al., 2012). The study found no difference in the proportion able to use words at the time of study, who ever babbled or spoke, between those with and without large deletions (Bebbington et al., 2012). A study using data from the Natural History Study grouped the mutations of 638 females as either mild (p.Arg133Cys, p.Arg294*, p.Arg306Cys and 3' truncations) or severe (p.Arg106Trp, p.Thr158Met, p.Arg168*, p.Arg255*, p.Arg270* and large deletions) (Neul et al., 2014). The authors found that a smaller proportion of females in the severe group were able to follow commands that were supported by gestures. No other significant relationships between genotype and communication abilities were found (Neul et al., 2014). According to these findings we might expect females with a p.Arg133Cys mutation to be more likely to retain the ability to use speech and females with a p.Arg207*, p.Arg255* or p.Arg168* mutation to be less likely to acquire or retain the ability to use speech. However all of these studies investigated relationships between *MECP2* mutation type and the performance of communication only at the time of study, no studies investigated relationships with speech language regression or the performance of communication prior to regression.

Two identified studies investigated relationships between aspects of motor ability and communication (Bartolotta et al., 2011; Cass et al., 2003). Over half (58%, 82/141) of the respondents to an online survey of parents and professionals caring for a female with Rett syndrome strongly agreed that apraxia limits the ability to communicate (Bartolotta et al., 2011). Furthermore, 57% of respondents reported that the female required a delay of 11 seconds or more to generate a response, possibly due to her apraxia. This study relied on the recall of survey respondents and therefore may not present an accurate picture of the amount of delay required for girls and women with Rett syndrome to respond. There remains a need to measure this delay using different methodologies, such as analysis of video data, to accurately identify the amount of time girls and women with Rett syndrome require to generate a communicative response. In a UK study (n=87), using data from caregivers, medical reports and direct observation and assessment by health professionals, more severe oral-motor dysfunction was associated with poorer scores on a communication measure. The measure included rating of the ability to point with eyes, make choices and understand cause and effect (Cass et al., 2003). However the psychometric properties of the communication measure were not reported in the publication so it is unclear how well the individual items represent overall communication performance. It may have been more meaningful to assess the relationships between oral-motor dysfunction and specific items, such as the ablity to point with eyes or make choices.

One study of 18 females with Rett syndrome aged seven to 21 years assessed relationships between the ability to complete receptive communication tasks and age of onset of epilepsy, seizure frequency and electroencephalography (EEG) stage (Vignoli et al., 2010). The receptive task required the female to recognise (i.e. look at dog), match pairs (i.e. look at the one that is the same) and semantically categorise (i.e. look at the one that is similar) three groups of pictures (fruit, animals and emotions) displayed on an eye gaze device. EEG stage was categorised according to Glaze and colleagues (1987) as either EEG stage III) moderate to marked slowing of background activity with dominant theta and delta activity or stage IV) no occipital dominant rhythm and marked slowing of background activity (Vignoli et al., 2010). Findings suggested that a later onset of epilepsy, less frequent seizures and EEG stage III were associated with better ability to recognize pictures, match pairs and to semantically categorise animals; and the ability to recognize emotions. Also as EEG abnormalities became more diffuse and multifocal, the ability to recognise, match and categorise fruit decreased (Vignoli et al., 2010). A Dutch study using caregiver report to describe communication abilities in 120 females aged five to 55 years found those without epilepsy used specific communication modalities, such as approaching and distancing from a person and taking objects, more for some communication functions than those with epilepsy (Didden et al., 2010). Yet in the previously described UK study by Cass and colleagues (2003), no relationship between history of epilepsy and communication was found. This study also found no relationship between the severity of breathing abnormalities and communication. The variation in sample sizes, participant ages and methods used to measure epilepsy across these studies makes it difficult to make conclusions and generalisations to the greater population of girls and women with Rett syndrome.

2.3.2.2 Activities and participation

Females with Rett syndrome commonly experience limitations in a range of activities including hand function, mobility and self-care and these limitations may impact their communication. Cass' (2003) UK study found that increased scores in self-care dependency, hand function and mobility, representing better abilities, were correlated with better communication scores. However, as previously described in relation to the communication measure, the psychometric properties of the hand function, mobility and self-care measures were not reported in this publication, limiting the strength of the results from this study. Respondents to Bartolotta's (2011) online survey that agreed the female with Rett syndrome they cared for used single words to communicate, were likely to also agree that she could follow one-step commands and used multiple modalities for communication. The survey also found that a history of

previous speech use was associated with the ability to use speech at the time of the study. Although only two identified studies examined relationships between limitations in activity performance and communication, they provide some early evidence that better performance in activities indicates better communication abilities (Bartolotta et al., 2011; Cass et al., 2011). Future research would benefit from utilising reliable and valid measures of hand function, mobility and self-care in Rett syndrome such as the gross motor ability measure developed by the Australian Rett Syndrome Study team (Downs, Bebbington, Jacoby, et al., 2008; Foley et al., 2011).

The context of communication activities may also impact the success of communication. A study of eight girls participating in familiar and unfamiliar activities found that generally girls were more likely to persist with their communication when familiar, as opposed to unfamiliar, activities were interrupted and stopped by a communication partner (Hetzroni & Rubin, 2006). Three other studies used similar procedures to investigate relationships between reading familiar and unfamiliar storybooks and communication outcomes (Koppenhaver, Erickson, Harris, et al., 2001; Koppenhaver, Erickson, & Skotko, 2001; Skotko et al., 2004). Some of the same participants may have been included across the studies that ranged in sample size from three to six and age from three to seven years. In contrast to Hetzroni & Rubin's study (2006), these studies found no difference in the frequency of symbolic communication produced by the girl according to whether she was read a familiar or unfamiliar storybook (Koppenhaver, Erickson, Harris, et al., 2001; Koppenhaver, Erickson, & Skotko, 2001; Skotko et al., 2004). Another study investigated the communication of three girls during a structured (e.g. storybook reading), unstructured (e.g. giving the girl a toy to play with) and daily living activity (e.g. feeding). The study found that girls were given the greatest opportunities for communication during the daily living activity, followed by the structured activity however an increased opportunity for communication did not correspond with increased rate of expressive communication by the girls with Rett syndrome (Ryan et al., 2004). These findings suggest that familiar and daily living activities may present the best opportunities for communication for girls and women with Rett syndrome, although the evidence is limited due to small sample size.

2.3.2.3 Environmental factors

Interventions, the characteristics and perceptions of the communication partner, and place of residence of the girl or woman are environmental factors that may influence communication outcomes. Communication partner training was evaluated in four studies with sample sizes

ranging from four to six girls with Rett syndrome, ranging in age from three to 15 years (Bartolotta & Remshifski, 2013; Koppenhaver, Erickson, Harris, et al., 2001; Koppenhaver, Erickson, & Skotko, 2001; Skotko et al., 2004). Three of these studies used the same intervention procedures and it is unclear from their methods whether new participants were recruited for each study or whether the same participants were used across the studies (Koppenhaver, Erickson, Harris, et al., 2001; Koppenhaver, Erickson, & Skotko, 2001; Skotko et al., 2004). These three studies investigated the impact of communication partner training within storybook reading interactions between mothers and their daughters (Koppenhaver, Erickson, Harris, et al., 2001; Koppenhaver, Erickson, & Skotko, 2001; Skotko et al., 2004) and the fourth study investigated the impact of training during mealtime interactions between school staff and girls with Rett syndrome (Bartolotta & Remshifski, 2013). Across all four studies communication partner training was individualised to the assessed needs of the girl, their communication partner and the context of the interaction, and included strategies such as waiting and looking for a response, and providing opportunities to use aided augmentative and alternative communication (AAC) (Bartolotta & Remshifski, 2013; Koppenhaver, Erickson, Harris, et al., 2001; Koppenhaver, Erickson, & Skotko, 2001; Skotko et al., 2004). Aided AAC refers to any external item used to aid communication (e.g. communication boards or books, eye gaze computer technology) (Speech Pathology Australia, n.d.)

Following training to support communication during mealtimes, Bartolotta and Remshifski (2013) reported that the girls' number of communicative attempts and the number of communication partner responses increased. One girl was also able to transfer the use of her AAC device into other classroom activities. In the remaining three studies communication partner training was provided in parallel with the use of resting hand splints and low technology AAC systems such as selecting symbols to communicate (Koppenhaver, Erickson, Harris, et al., 2001; Koppenhaver, Erickson, & Skotko, 2001; Skotko et al., 2004). In two of the three studies, the frequency of symbolic communication produced per minute by the girl with Rett syndrome increased with the provision of aided AAC and communication partner training, but not with splinting the non-dominant hand (Koppenhaver, Erickson, Harris, et al., 2001; Koppenhaver, Erickson, & Skotko, 2001). The outcomes of the final study varied widely between the four girls, making it difficult to draw conclusions about the relationship between splinting, the provision of aided AAC and parent training, and communication outcomes (Skotko et al., 2004). Due to very small sample sizes and study design of the four studies, it is difficult to know if observed increases in communication were solely due to communication partner training or if other factors not studied may have contributed.

Other interventions that may have an impact on communication abilities in Rett syndrome include the provision of aided AAC (Stasolla et al., 2014) and other assistive technology (Stasolla et al., 2015). Two forms of aided AAC, picture exchange communication systems (PECS) and vocal output communication aids (VOCA) were provided to three girls with Rett syndrome aged eight to 10 years within the home environment (Stasolla et al., 2014). The use of PECS and VOCA resulted in increased frequencies of requested and chosen items across all participants and VOCA appeared to be preferred in comparison to PECS by two of the girls (Stasolla et al., 2014). Another study provided assistive technology consisting of containers equipped with photocells that once triggered, by placing an item in the container, activated an activity on a laptop (Stasolla et al., 2015). This study included three girls aged nine to 12 years who used the assistive technology to make a choice between activating a song, video or coloured lights on a laptop. Findings suggested the girls were successful in learning to place an item in one container, out of a choice of three, to activate an activity. However, due to the study design it is not known if the girls placed items in containers they truly preferred, or whether they placed an item in a container at random.

The containment of hand stereotypies (Fabio et al., 2009; Fabio et al., 2011), the use of positive reinforcement within communication focused tasks (Elefant & Wigram, 2005; Fabio et al., 2011; Hetzroni et al., 2002), functional communication training (Byiers et al., 2014) and cognitive rehabilitation (Fabio et al., 2013) are other interventions that may improve communication abilities in girls and women with Rett syndrome. The containment of hand stereotypies during receptive communication tasks improved the rate of learning in two studies of 10 (Fabio et al., 2009) and 12 females with Rett syndrome (Fabio et al., 2011). Furthermore, Fabio et al., (2011) investigated the relationship between the provision of positive reinforcement by the communication partner following a correct response, and also found this improved learning. (Fabio et al., 2013). Hetzroni, Rubin and Konkol (2002) also demonstrated that reinforcement, delivered as visual and auditory feedback on a computer program, had a positive impact on learning in receptive communication tasks in three girls. Reinforcement also improved learning and the ability to confirm song choices in seven girls (Elefant & Wigram, 2005). In this study reinforcement consisted of the girls' chosen song being sung to her, by a music therapist accompanied by a guitar, following the confirmation of song choice. Functional communication training was found to be effective in three females with Rett syndrome aged 15, 27 and 47 years, with each learning to activate a switch to communicate their chosen function (Byiers et al., 2014). The use of cognitive rehabilitation based on Feuerstein, Rand and Rynders' (1988) modifiability and mediated learning theory was described in a longitudinal single case study (Fabio et al., 2013). Results indicated the

participant was taught to recognise 16 words, 18 syllables and 19 letters from the ages of eight to 21 years. Music therapy (Yasuhara & Sugiyama, 2001) and combined music therapy and physiotherapy may also impact communication abilities (Elefant & Lotan, 2004). A case series of three girls showed improvements in communication outcomes for two of the girls following individualised music therapy sessions although specific detail of the therapeutic activities was not provided (Yasuhara & Sugiyama, 2001). Following a joint physiotherapy and music therapy program a nine year old girl with Rett syndrome, who had previously been unable to make choices, was able to make some choices using symbols (Elefant & Lotan, 2004). Although these studies provide some promising results, they were all limited due to their small sample sizes. It is not clear if these interventions may only be relevant for particular groups of girls and women, for example those with a particular genotype or phenotype, or if equal success could be expected across the population of girls and women with Rett syndrome.

Characteristics or perceptions of communication partners might also influence the communication outcomes of females with Rett syndrome (Bartolotta et al., 2011; Ryan et al., 2004; Sigafoos, Woodyatt, Tucker, et al., 2000). Generally communicative interactions that involved communication partners modifying their approach to interaction were more likely to elicit communicative responses from the females with Rett syndrome. This included communication partners who initiated communication and talked to, touched or offered items to the girl (Sigafoos, Woodyatt, Tucker, et al., 2000) and presented objects in addition to the use of language during everyday activities such as eating (Ryan et al., 2004). More parents than professionals participating in Bartolotta's (2011) survey strongly agreed that familiar people can interpret the communication attempts and most people underestimate the abilities of girls with Rett syndrome. Furthermore, a survey of Swedish speech-language pathologists working in Rett syndrome found that most (73%, 47/64) felt pictures/objects of reference were a useful intervention (Wandin et al., 2015). Smaller proportions felt other interventions such as visual support (58%, 37/64), single message electronic devices (47%, 30/64) and communication charts/books (34%, 22/64) were useful. Most (73%, 37/64) also felt communication aids made choice making more clear and occur more frequently. Didden et al. (2010) investigated relationships between place of residence and communication with caregivers completing questionnaires including the Inventory of Potential Communicative Acts (IPCA) (Sigafoos, Woodyatt, Keen, et al., 2000). It found that in a sample of 120 females with Rett syndrome, those who lived at home used eye gaze more for a number of communicative functions as opposed to those who lived in residential care (Didden et al., 2010). It is important to remember that communication partners may interpret the behaviour of the girl or woman with Rett syndrome differently so this can be taken into account in the management of

communication abilities. Also the environment in which the girl or woman lives needs to be considered as it may impact on the availability of reinforcement and learning opportunities for communication.

2.3.2.4 Personal factors

The literature presents mixed findings regarding the influence of the age of the girl or woman with Rett syndrome on communication abilities. Two studies investigated aspects of communication over time in the first 24 months of life using video data of girls who were later diagnosed with Rett syndrome(Marschik, Bartl-Pokorny, et al., 2014; Townend, Bartl-Pokorny, et al., 2015). Townend , Bart-Pokorny et al. (2015) investigated the frequency with which girls, who were later diagnosed with typical Rett syndrome (n=10) or the preserved speech variant (n=5), responded to their name at different time points between the ages of 5 to 24 months. The study found those later diagnosed typical Rett syndrome responded more frequently than the preserved speech variant group between the ages of five to eight months but those who were later diagnosed with preserved speech variant responded more frequently over time. Marschik, Bartl-Pokorny and others (2014) compared the presence of communicative forms present in videos of a typically developing girl, a girl later diagnosed with the preserved speech variant and a girl later diagnosed with typical Rett syndrome at multiple time points. The girls were aged between nine and 24 months in the videos. The forms of communication identified for the different girls varied, however it appeared the girl later diagnosed with the preserved speech variation increased her perlinguistic vocalisations over time (Marschik, Bartl-Pokorny, et al., 2014).

The largest study investigating age and communication abilities (n=120) found those aged over 22 years used some communicative forms for specific functions significantly less than younger girls (Didden et al., 2010). For example, only 28% of those aged 22 years or older used eye gaze for choice making compared to 63% of those aged 4 – 12 years and 47% of those aged 13 – 21 years. Cass' (2003) UK study found that those aged below 20 years had higher communication composite scores, representing better abilities, however this finding was not statistically significant. Furthermore the age of onset of regression was not related to communication score in this study (Cass et al., 2003). However, how the age of onset of regression was calculated or specific data for this variable was not presented in the study.

Findings from other cross-sectional studies with smaller sample sizes and findings from case studies provide mixed evidence for a link between age and communication abilities. Two cross

sectional studies reported on the same group of participants at two different time points (Halbach et al., 2008; Halbach et al., 2013). At the first time point, parents of 10 females reported an improvement in communication from the age of 10 years and three parents reported a decline (Halbach et al., 2008). In the follow up study, three parents reported an improvement in communication since the previous questionnaire was administered five years earlier and three parents reported a decline in these abilities (Halbach et al., 2013). One study (n=10) found no relationship between age and performance in a receptive task (Fabio et al., 2009) while another (also n=10) found a correlation between increasing age and the ability to correctly perform one of 10 receptive tasks such as "look at yellow" or "look at triangle" (Velloso et al., 2009). Yamashita and others (2001) reported on five females, aged nine to 21 years, labelled as the preserved speech variant of Rett syndrome. They reported all acquired early words and had words at the time of the study, with one female never experiencing a regression in her speech. A longitudinal case study found that reading ability improved with time and intervention over a 13 year period in one girl with a p.Arg306Cys mutation (Fabio et al., 2013). Another case study found a recovery of speech after the regression period in an 11 year old girl with a large intragenic deletion (c.378-43_964delinsGA) and increasing complexity in speech with age (Marschik, Vollmann, et al., 2014). The development of a girl with a p.Arg133Cys mutation, who used words prior to regression, was described in another case study. Regression occurred at five years of age and the girl began talking again a year after experiencing an initial regression but at a poorer level than previously (Nielsen et al., 2001). Evidently the literature presents conflicting findings with no clear trend between age and communication abilities.

2.4 Summary

A number of body functions and structures, activities and environmental and personal factors may impact the communication abilities of girls and women with Rett syndrome. It is likely that many of these factors interact or have relationships with each other and this needs to be considered in future research and when clinically assessing the communication abilities of this population. In particular it is well known that genotype influences numerous functional abilities including mobility and hand function (Bebbington et al., 2008; Cuddapah et al., 2014). For example those with a p.Arg133Cys mutation may be the most likely to have words in comparison to those with other mutations (Bebbington et al., 2008; Leonard et al., 2003; Neul et al., 2008). However girls and women with this mutation are also likely to experience better motor abilities which may impact their ability to use other modalities such as body movements and hand use for communication (Bebbington et al., 2008). Furthermore the strategies used

across a number of interventions such as reinforcing appropriate communicative behaviours, may be beneficial for the communication abilities of girls and women with Rett syndrome.

Due to the generally poor methodological quality of reviewed studies, findings of the current literature are difficult to interpret and have limited generalisabiltiy to the larger population of girls and women with Rett syndrome. This was largely as a result of small sample sizes with a lack of genotypic information and limited representativeness, and inadequate descriptions of the tool or procedure used to measure communication or factors such as motor abilties. Nevertheless this literature review provides an understanding of current knowledge on the numerous barriers and facilitators to successful communication in females with Rett syndrome that should be considered when assessing communication abilities and developing and prescribing communication interventions.

Table 1. Summary of reviewed articles evaluating the relationship between communication abilities and factors in females with Rett syndrome (n=38).

First author (Year)[a]	Methods		Participants			Communication measure	Factor/s influencing communication			
	Study Design & Level of Evidence	Data collection method	N	Age of RTT[b] cases (years)	*MECP2* status		Body function & structure	Activities & participation	Environmental factors	Personal factors
Bartolotta (2013)	Case series pre-test/ post-test Level IV	Video recorded feeding interaction	4 RTT cases	5, 10, 11 & 15[c]	Not stated	Number of student & feeder bids for communication, student & feeder responses, & feeder comments not requiring a response	-	-	Intervention: communication partner training	-
Bartolotta (2011)	Cross-sectional Level IV	Questionnaire completed by parents, speech-language pathologists or teachers	141 respondents	Groups: 0-3 15% 4-7 33% 8-13 24% 13-20 17% 21≤ 11%	Not stated	Modalities used to communicate, time taken to respond and ability to follow commands	Apraxia	Speech ability	Communication partner perceptions	-
Bebbington (2008)	Cross-sectional Level IV	Questionnaire completed by parents or clinicians	276 RTT cases	Range: 1 – 45[d]	276/276 positive	Speech ability coded as: sentences, phrases, single words, lost all speech or never talked	*MECP2* mutation type	-	-	-
Bebbington (2012)	Cross-sectional Level IV	Questionnaire completed by parents or clinicians	974 RTT cases	Range: 1 - 49 Mean: 11 Median: 9	974/974 positive	Speech ability coded as: preserved, single words, babbling or none	*MECP2* mutation type	-	-	-

First author (Year)[a]	Methods		Participants			Communication measure	Factor/s influencing communication			
	Study Design & Level of Evidence	Data collection method	N	Age of RTT[b] cases (years)	*MECP2* status		Body function & structure	Activities & participation	Environmental factors	Personal factors
Byiers (2014)	Case series pre-test/ post-test Level IV	Mixed methods: Interview with primary caregiver, direct observation and analog functional analyses	3 RTT cases	15, 27 & 47	2 cases not tested & 1 case positive	Frequency counts for the target behaviours and independent switch activation	-	-	Intervention: functional communication training	-
Cass (2003)	Cross-sectional Level IV	Mixed methods: Parent report, medical report review, direct observation & assessment by health professionals	87 RTT cases	Mean: 27 ± 7 Groups: 2-4 30% 5-9 28% 10-19 13% 20-44 20%	Not stated	A scale assigning one point to the presence of the following abilities: eye-pointing, understanding of cause/effect, ability to make choices, ability to indicate 'more' and use of words (with or without meaning)	Oral motor function, breathing abnormalities & epilepsy	Mobility, hand function and self-care abilities	-	Age at study and onset of regression
Chae (2004)	Cross-sectional Level IV	Not reported	42 RTT cases, only 21 included in phenotypic analysis	At least 5 years old at data collection	30/42 positive	Speech ability coded as: some comprehensible words, a few words or absent	*MECP2* mutation	-	-	-
Didden (2010)	Cross-sectional Level IV	Questionnaire completed by parents or jointly by parents and staff member if the female lived in a residential facility	120 respondents	Range: 5 – 55 Mean: 21 ± 12	89/120 positive	Inventory of Potential Communicative Acts (Sigafoos et al., 2000)	Epilepsy	-	Place of residence	Age

First author (Year)[a]	Methods		Participants			Communication measure	Factor/s influencing communication			
	Study Design & Level of Evidence	Data collection method	N	Age of RTT[b] cases (years)	*MECP2* status		Body function & structure	Activities & participation	Environmental factors	Personal factors
Elefant (2004)	Case study	Not reported	1 RTT case	9	Not stated	Description of the ability to make choices	-	-	Intervention: Dual music and physical therapy	-
Elefant (2005)	Case series Level IV	Observation of performance in structured communication tasks	7 RTT cases	Range: 4 - 10	Not stated	Frequency of the ability to confirm song choice	-	-	Intervention: Music therapy and positive reinforcement	-
Fabio (2009)	Case series pre-test/ post-test Level IV	Video recorded structured communication tasks	10 RTT cases	Range: 5 - 26 Mean: 11 ± 7	10/10 positive	The number of attempts and correct answers	-	-	Intervention: containment of stereotypies	Age
Fabio (2011)	Case series pre-test/ post-test Level IV	Mixed methods: video recorded structured communication tasks & administration of the Vineland Adaptive Behavior Scales via parent interview	12 RTT cases	Range: 6 - 26 Mean: 13 ± 6	12/12 positive	The number of attempts and correct answers and scores on the Vineland Adaptive Behavior Scales	-	-	Intervention: containment of stereotypies and positive reinforcement	-
Fabio (2013)	Case study	Observation of performance in structured communication tasks	1 RTT case	21	1/1 positive	The number of attempts required to learn to read words, syllables and letters	-	-	Intervention: Cognitive rehabilitation training	Age

First author (Year)[a]	Methods		Participants			Communication measure	Factor/s influencing communication			
	Study Design & Level of Evidence	Data collection method	N	Age of RTT[b] cases (years)	*MECP2* status		Body function & structure	Activities & participation	Environmental factors	Personal factors
Halbach (2008)	Cross-sectional Level IV	Questionnaire completed by parents and/or a support worker or a physician	53 respondents	Range: 16 - 53 Groups: 16-20 21% 20-30 45% 30≤ 34% Mean: 27 ± 8	37/53 tested 31/37 positive	Ability to use spoken language and/or signals	-	-	-	Age
Halbach (2013)	Cross-sectional Level IV	Questionnaire completed by parents and/or a support worker or a physician	37 respondents	Range: 21 – 46 Groups: 16-20 30% 20-30 41% 30≤30% Mean: 31 ± 7	29/37 tested 24/29 positive	Ability to use spoken language and/or signals	-	-	-	Age
Hetzroni (2002)	Case series pre-test/ post-test Level IV	Observation of performance in structured communication tasks	3 RTT cases	8, 9 & 10	Not stated	Ability to identify the correct symbol in response to verbal instruction	-	-	Intervention: positive reinforcement	-
Hetzroni (2006)	Case series Level IV	Video recorded structured communication tasks	8 RTT cases	Mean 8.75 ± 2.12 years 4-11 years	Not stated	Modalities used to communicate	-	Activity context: familiar & unfamiliar	-	-

First author (Year)[a]	Methods		Participants			Communication measure	Factor/s influencing communication			
	Study Design & Level of Evidence	Data collection method	N	Age of RTT[b] cases (years)	*MECP2* status		Body function & structure	Activities & participation	Environmental factors	Personal factors
Huppke (2002)	Cross-sectional Level IV	67 cases examined by health professionals in a Neuropaediatric Department, 68 had data obtained by questionnaire and telephone interviews but not clear with whom	123 RTT cases	All data reported pertained to the girls' at 5 years of age	123/123 positive	Speech ability coded as: more than 10 words at age 5 years, loss of ability to speak or never spoken	*MECP2* mutation	-	-	-
Koppenahver, Erickson, Harris, et al. (2001)	Case series pre-test/ post-test Level IV	Multiple video recorded story-book reading interactions (one interaction was assessed)	6 RTT cases	Range: 3 - 7	Not stated	Communication modalities and functions	-	Activity context: familiar & unfamiliar	Intervention: hand splints, aided AAC & communication partner training	-
Koppenahver, Erickson & Skotko (2001)	Case series pre-test/ post-test Level IV	Multiple video recorded story-book reading interactions (all assessed)	4 RTT cases	Range 3 - 7	Not stated	Communication modalities and functions	-	Activity context: familiar & unfamiliar	Intervention: hand splints, aided AAC & communication partner training	-
Leonard (2003)	Cross-sectional Level IV	Mixed methods: Questionnaire completed by caregiver or clinician, interview with parents or clinical data for non-Australian cases	121 RTT cases	R133C cases mean: 15 ± 7 Other cases mean: 14 ± 6	121/121 positive	Speech ability coded as: more than single words, single words, more than no vocalisation but no single words, lost speech or never acquired	*MECP2* mutation	-	-	-

First author (Year)[a]	Methods		Participants			Communication measure	Factor/s influencing communication			
	Study Design & Level of Evidence	Data collection method	N	Age of RTT[b] cases (years)	*MECP2* status		Body function & structure	Activities & participation	Environmental factors	Personal factors
Marschik, Bartl-Pokorny, et al (2014)	Case series Level IV	Family videos of RTT cases prior to diagnosis	2 RTT cases 1 typically developing female	Range: 0 – 2	2/2 positive	Communication modalities and functions coded according to the IPCA	-	-	-	Age
Marschik, Vollmann, et al (2014)	Case study Level IV	Retrospective video analyses, medical history data, parental checklists and dairies, standardised test on vocabulary and grammar, spontaneous speech samples and picture stories to elicit narrative competencies	1 RTT case	11 years at study	1/1 positive	Communication modalities & functions	-	-	-	Age
Neul (2008)	Cross-sectional Level IV	Clinical evaluation	245 RTT cases	Mean: 11	236/245 positive	Speech ability coded as: preserved, short phrases, single words, babbling/ vocalisation, or screaming or no utterances	*MECP2* mutation	-	-	-

First author (Year)[a]	Methods		Participants			Communication measure	Factor/s influencing communication			
	Study Design & Level of Evidence	Data collection method	N	Age of RTT[b] cases (years)	*MECP2* status		Body function & structure	Activities & participation	Environmental factors	Personal factors
Neul (2014)	Cross-sectional Level IV	Interview with primary caregiver & review of medical evaluations	638 RTT cases	Not clearly stated	613/638 positive	Attainment & loss of social smile, coo, babble, single words, phrases, gestures, points for wants, follow command with gesture & follow command without gesture	*MECP2* mutation	-	-	-
Nielsen (2001)	Case study	Not clearly reported	2 RTT cases, only 1 with communication data	Not clearly stated	2/2 positive	Description of use of speech	-	-	-	Age
Ryan (2004)	Case series Level IV	Video recorded interactions	3 RTT cases	9, 14 & 16	Not stated	Partner & student cues, partner & student responses, behaviours not requiring a response, orientating cues	-	Activity context: structured, unsctructured and daily living activity	Communication partner characteristics	-
Sigafoos (2000)	Case series Level IV	Video recorded interactions & structured communication tasks	3 RTT cases	10, 18 & 19	Not stated	Communication modalities	-	-	Communication partner characteristics	-

First author (Year)[a]	Methods		Participants			Communication measure	Factor/s influencing communication			
	Study Design & Level of Evidence	Data collection method	N	Age of RTT[b] cases (years)	*MECP2* status		Body function & structure	Activities & participation	Environmental factors	Personal factors
Skotko (2004)	Case series pre-test/ post-test Level IV	Multiple video recorded story-book interactions (all assessed)	4 RTT cases	Range: 3 - 7	Not stated	Communication modalities and functions, and reading behaviours	-	Activity context: familiar & unfamiliar	Intervention: hand splints, aided AAC & communication partner training	-
Stasolla (2014)	Case series pre-test/ post-test Level IV	Video recorded structured communication tasks	3 RTT cases	8, 9 & 10	Not stated	Frequency of items requested using PECS[g] and VOCA[h]	-	-	Intervention: PECS and VOCA	-
Stasolla (2015)	Case series pre-test/ post-test Level IV	Video recorded structured communication tasks	3 RTT cases	9, 10 & 12	Not stated	Frequency of placement of object into a container to request an activity	-	-	Intervention: Assistive technology consisting of container equipped with photocells	-
Townend, Bartl-Pokorny, et al (2015)	Case series Level IV	Family videos of RTT cases prior to diagnosis	15 RTT cases	Range: 0 – 2	15/15 positive	The frequency of responding to their name when it was called	-	-	-	Age
Velloso (2009)	Case series Level IV	Eye fixation time using eye gaze technology	10 RTT cases	Range: 4 - 12 Mean: 9 ± 3	8/10 positive	The number of correct answers to verbal instructions	-	-	-	Age

First author (Year)[a]	Methods		Participants			Communication measure	Factor/s influencing communication			
	Study Design & Level of Evidence	Data collection method	N	Age of RTT[b] cases (years)	*MECP2* status		Body function & structure	Activities & participation	Environmental factors	Personal factors
Vignoli (2010)	Cross-sectional Level IV	Eye fixation time using eye gaze technology	18 RTT cases	Range: 7 - 21 Mean: 14 ± 5	18/18 positive	The number of correct answers to verbal instructions	Epilepsy	-	-	
Wandin (2015)	Cross-sectional Level IV	Questionnaire completed by SLPs	77 respondents 64 respondents to question of interest	Not reported	Not stated	The perceived usefulness of different communication aids	-	-	Intervention: Use of communication aids	-
Weaving (2003)	Cross-sectional Level IV	Questionnaire completed by caregiver or clinician	213 RTT cases, only 98 with phenotypic data	Not reported	138/213 positive 75/98 with pheno-typic data positive	Language and non-verbal communication	*MECP2* mutation	-	-	-
Yamashita (2001)	Case series Level IV	Not clearly reported	5 RTT cases	9, 9, 10, 20 & 21	5/5 positive	Ability to use speech	-	-	-	Age
Yasuhara (2001)	Case series pre-test/ post-test Level IV	Video recorded music therapy sessions	3 RTT cases	4, 5, 6	Not stated	Use of language	-	-	Intervention: Music therapy	-

[a] Studies by the same first author published in the same year include subsequent author surnames to distinguish studies; [b] RTT = Rett syndrome; [c] The age of the oldest participant was checked with the authors due to discrepancy in data reported in the article; [d] Does not include four cases with date of birth unspecified

Chapter 3: Methodology

This chapter provides an overview of the methodology underpinning this research. In doing so it outlines the design of each study, describes the databases used as the source of data and provides the rationale for the case inclusion criteria used within the research. The first study included in this thesis was a qualitative investigation involving interviews with parents with a daughter with Rett syndrome, the second and third studies were cross-sectional and utilised questionnaire data while the final study used video data at one time point to describe choice making.

3.1 Data sources

Data was sourced from two databases, the population-based Australian Rett Syndrome Datebase (ARSD and InterRett. These databases were created in response to a lack of information on individuals with Rett syndrome and therefore the clear need to develop large repositories of data to inform the management of Rett syndrome in Australia and internationally. The use of large repositories of data is important, particularly in the study of rare diseases, enabling meaningful statistical research (Leonard et al., 2013). Furthermore the ARSD is the only population-based database of individuals with Rett syndrome in the world. Therefore data from the ARSD is unbiased in inclusion and more generalisable. Both databases allowed diagnosis of Rett syndrome to be verified with available genetic data and provided access to a large sample of girls and women with Rett syndrome that may have not been attained using other recruitment methods. Being able to verify diagnosis of Rett syndrome through genetic testing and conduct studies with large sample sizes improves the generalisability of the research findings.

3.1.1 The Australian Rett Syndrome Database (ARSD)

The ARSD is a population-based database of Australian girls and women with Rett syndrome born since 1976. Established in 1993 by Dr Helen Leonard, the database continues to collect longitudinal data on registered cases andto this date, is the only population-based database of Rett syndrome in the world. Cases are referred to the database from a variety of sources including the Australian Paediatric Surveillance Unit, the Rett Syndrome Association of Australia and community based clinicians (Leonard, 1996). The ARSD collects data on numerous aspects of Rett syndrome and its impact on the individual and their family. Data is collected using a variety of methods including questionnaires (Downs, Bebbington, Woodhead, et al., 2008), video-based evaluations (Fyfe et al., 2007) and interviews with caregivers

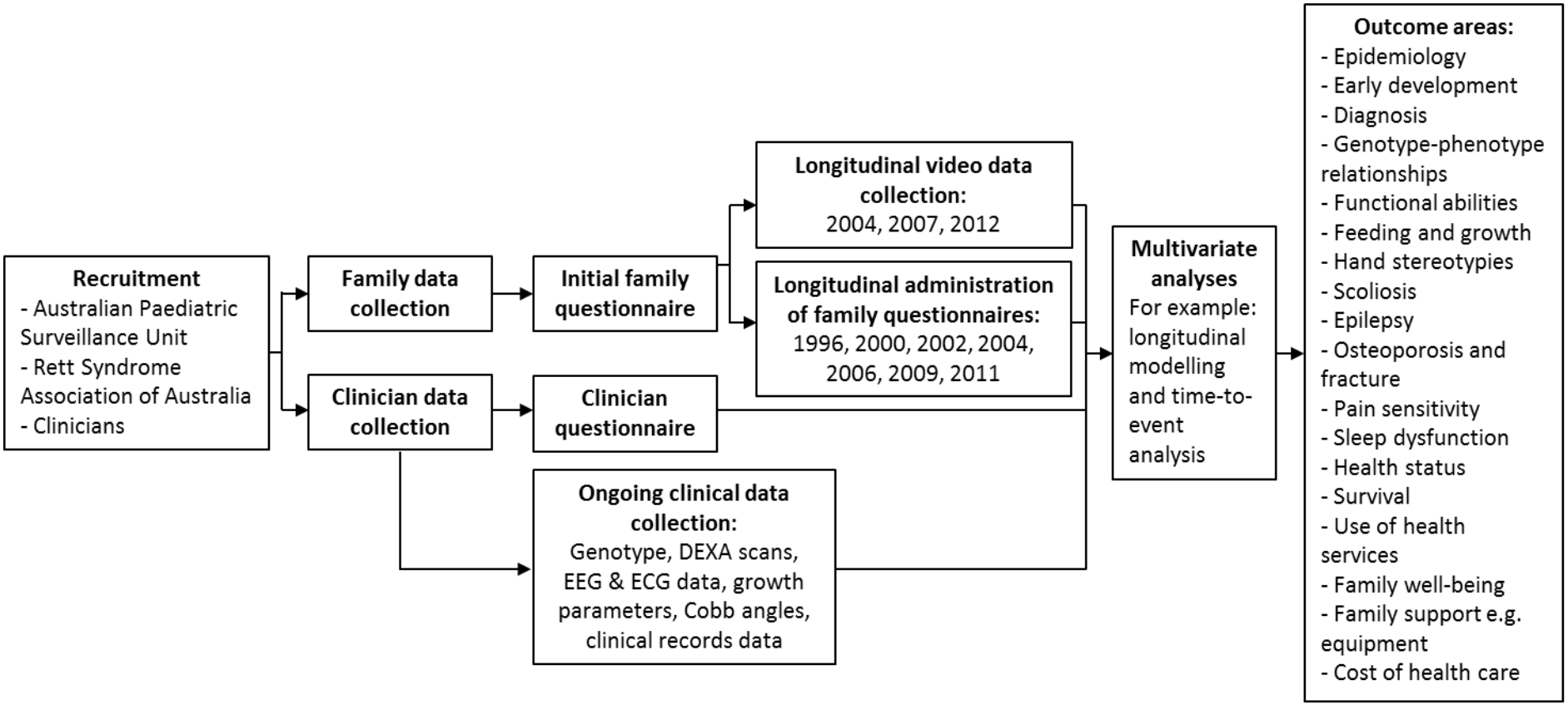
(Walker, Crawford, & Leonard, 2014). The database has allowed for the study of a variety of outcome areas including epidemiology, genotype-phenotype relationships and functional abilities (Figure 1). The database is housed at the Telethon Kids Institute in Perth, Western Australia.

Upon enrolment into the ARSD an initial questionnaire is completed by the girl's primary caregiver and clinician. The initial questionnaire completed by the primary caregiver collects information on the mother's pregnancy, the child's birth, early development and their current level of functioning. This questionnaire includes questions about the child's regression in speech-language abilities and her level of speech-language abilities prior to and after this regression.

Since the year 2000, follow-up questionnaires have been distributed to participating families approximately every two years. These questionnaires gather information about everyday functioning, specific Rett syndrome behaviors, medical conditions, such as epilepsy, use of health services and resources such as therapy and respite, and family functioning. Everyday functioning was measured using questions developed based on the paediatric version of the Functional Independence Measure (WeeFIM) (Msall et al., 1994).

The video-based evaluation tool (Fyfe et al., 2007) was designed to collect information on the abilities of girls and women with Rett syndrome who have a range of functional activities. The tool is broadly based on the domains of the WeeFIM (Msall et al., 1994). It comprises of two components, a filming protocol and a parent-report checklist called the Functional Ability Checklist (FAC). The filming protocol contains six sections: communication, eating and drinking, hand movements and functions, personal care, mobility, and breathing patterns and sleeping. The communication section of the filming protocol asks caregivers to film the girl or woman making a choice between two items, their reaction to placing an object in front of them but slightly out of reach and their reaction to the caregiver stopping an activity such as a movie or feeding. The FAC was developed to be used in conjunction with the filming protocol and asked parents to provide further detail on their daughter's performance in the filmed skill areas. The communication section of the FAC includes 14 items from the Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist (CSBS DP ITC) (Wetherby & Prizant, 2002). The video-based evaluation tool was developed in consultation with relevant health professionals and piloted with families caring for a girl or woman with Rett syndrome. Families participating in the ARSD have been asked to complete a video-based evaluation at three points in time in 2004, 2007 and 2012. Video data has previously been used to describe

Figure 1. Schemic diagram of the ARSD showing recruitment, longitudinal data collection from multiple sources, and multivariate analyses of outcomes.



DEXA = dual-energy X-ray absorptionmetry; ECG = electrocardiography (Downs & Leonard, 2013)

the changes over time in important functional abilities such as gross motor (Foley et al., 2011) and hand function domains (Downs, Bebbington, Kaufmann, & Leonard, 2010).

3.1.2 International Rett Syndrome Phenotype Database (InterRett)

InterRett was established in 2002 and collects cross-sectional data on girls and women with Rett syndrome from 54 countries around the world (Fyfe, Cream, de Klerk, Christodoulou, & Leonard, 2003; Louise et al., 2009). The majority of data come from the USA, Spain, France, China, Canada and the UK. The primary aim of InterRett is to increase the clinical understanding of Rett syndrome by creating a large international database of females with Rett syndrome to be used for research (Fyfe et al., 2003; Leonard et al., 2013). Cases are ascertained through international parent support groups, the email list serve RettNet (Leonard et al., 2004) and the submission of de-identified data from clinicians outside Australia (Louise et al., 2009). InterRett is also housed at the Telethon Kids Institute, Perth, Western Australia.

Primary caregivers and clinicians complete an initial questionnaire upon enrolment into InterRett. InterRett questionnaires are based on the ARSD initial questionnaire and therefore data collected from both databases is comparable. Australian families with a daughter with Rett syndrome born prior to 1976 may be included in InterRett.

3.2 Case inclusion criteria

Only female cases with a diagnosis of Rett syndrome, confirmed with the presence of a pathogenic *MECP2* mutation, were considered for inclusion in all four studies in this thesis. As outlined in the introduction chapter of this thesis, atypical forms of Rett syndrome have been suggested including the early seizure variant and congenital variant of Rett syndrome (Neul et al., 2010). However recent research has shown that these atypical forms have a different genetic etiology and should be considered separate diagnoses (Fehr et al., 2013; Kortüm et al., 2011). Furthermore the literature has described 57 cases of Rett syndrome in males, with varied phenotypic severity and about half of whom had a *MECP2* mutation (Reichow, George-Puskar, Lutz, Smith, & Volkmar, 2015). Therefore in order to ensure a more homogenous sample across the studies included in this thesis, only females with a diagnosis of Rett syndrome and a pathogenic *MECP2* mutation were included in analyses.

3.3 Study design

This thesis included both qualitative and quantitative cross-sectional studies to describe the performance of communication in girls and women with Rett syndrome and to investigate factors that are positively and negatively associated with communication performance. Specifically, one study involved interviews with parents with a daughter with Rett syndrome and the remaining studies involved quantitative analyses of questionnaire or video data. The inclusion of both qualitative and quantitative studies allowed communication performance to be examined from multiple perspectives. The quantitative data was used to develop a broad understanding of the performance of different communication tasks while the qualitative data was used to develop a deeper understanding of the area.

Following is a description of the methods used and the role of the candidate in each study. Please refer to Table 2 for an overview of the each study including the research objectives, study design, data source and the components of ICF-CY (World Health Organization, 2007) addressed.

3.3.1 Study 1 - Parental perspectives on the communication abilities of their daughters with Rett syndrome

The first study presented in this thesis used interviews with parents to answer two research questions (1) how do females with Rett syndrome communicate in everyday life? and (2) what factors act as barriers or facilitators to successful communication? This study provides valuable depth to the findings of the quantitative studies (studies 2 - 4) and is the first qualitative investigation of communication abilities in Rett syndrome.

Purposive selection of participants from the ARSD based on the age of the individual with Rett syndrome and her level of functional abilities as measured by the WeeFIM (Msall et al., 1994). Sixteen mothers, whose daughter had a pathogenic *MECP2* mutation and was living at home, were asked to participate. One mother declined this invitation. Therefore the mother and father of an Australian woman born prior to 1976 and who was participating in InterRett were recruited. In total 17 parents whose daughters were aged between two and 38 years at the time of study were recruited to participate in a semi-structured interview.

The ICF-CY (World Health Organization, 2007) informed the development of the interview guide. The use of the ICF-CY (World Health Organization, 2007) ensured questions concerning the different tasks involved in communication and the activity limitations and contextual factors that may influence the performance of these tasks were included. The guide was

piloted and adjusted according to feedback from three Australian mothers with a daughter with Rett syndrome who did not contribute data to the study. Interviews were recorded and transcribed verbatim. All participants received a copy of their interview transcript for checking and 12 parents provided additional information to be included in analysis.

Transcripts were analysed using directed content analysis (Hsieh & Shannon, 2005). This approach falls under the broader category of qualitative content analysis that is "a research method for the subjective interpretation of the content of text data through the systematic classification process of coding and identifying themes or patterns" (Hsieh & Shannon, 2005, p 1278). Specifically, directed content analysis involved using an existing theory or prior research to develop the initial coding framework prior to beginning data analysis. During data analysis additional codes that did not meet the initial coding framework were developed, for example a code for multiomodal communication, and the initial coding framework was revised and refined. Directed content analysis allows existing theories to be further explored and validated. This analytical approach has been used to explore a range of health issues such as risk factors for cardiovascular disease (Sabzmakan et al., 2014) and for hospital readmissions (Jeffs, Dhalla, Cardoso, & Bell, 2014).

In this study the ICF-CY (World Health Organization, 2007) and The Communication Matrix (Rowland, 2004) formed the basis of the development of the initial coding framework. The ICF-CY (World Health Organization, 2007) and the Communication Matrix (Rowland, 2004) were chosen to form the basis of the initial coding as they provide existing theory about the performance of communication and the factors that influence performance. Firstly, data on the performance of communication was coded as expressive or receptive communication in line with the ICF-CY classification of communication tasks "communicating - producing" and "communicating - receiving". The expressive communication data was then categorised as either the modality of communication (e.g. body movements) or function of communication (e.g. making choices) and receptive communication data was coded according to the modality of the message being received (e.g. understanding language). These subcategories were informed by The Communication Matrix (Rowland, 2004) Factors influencing the performance of communication were coded according to the relevant ICF-CY categories for body functions and structures (e.g. psychomotor control), activities and participation (e.g. mobility), environmental (e.g. attitudes) and personal factors (e.g. other medical conditions). For this coding detailed ICF-CY (World Health Organization, 2007) classification levels were used initially.

Each transcript was read line by line and coded according to this initial framework. The operational definitions of each code were developed by the candidate using the ICF-CY (World Health Organization, 2007) and the Communication Matrix (Rowland, 2004) and were reviewed by another researcher prior to analysis commencing. After applying the initial framework the data were reviewed to merge similar codes. All data were considered relevant and a new code that did not fit the initial framework was developed to reflect the multimodal aspect of communication. Initial coding was completed by the candidate and reviewed by two of the candidate's supervisors to ensure the credibility of results. NVivo 10 software(QRS International Pty Ltd, 2012) was used to manage and code transcripts.

The ability to use data from prexisting databases in this study allowed sampling to occur across ages and functional abilities, diagnosis of Rett syndrome to be confirmed with available genetic information and other data about the girls and women, such as the age of speech regression, to be used without the need to collect this information from parents during the interview. The candidate was responsible for the recruitment of participants from the databases, the development of the interview guide, and conducting and transcribing all interviews. The coding framework was developed and data analysis conducted by the candidate and reviewed by the candidate's supervisors to ensure credibility of the data. The candidate completed the first draft of the publication. The candidate's supervisors reviewed drafts and provided feedback for consideration by the candidate.

3.3.2 Study 2 - Aspects of speech-language abilities are influenced by *MECP2* mutation type in girls with Rett syndrome

The second study presented in this thesis described the performance of producing communication, in particular the ability to use speech and babble before and after speech-language regression. It also investigated relationships between the performance of speech-language tasks and *MECP2* mutation type. According to the ICF-CY (World Health Organization, 2007) a *MECP2* mutation is considered an impairment in body function and structure.

This study utilised data from both the InterRett questionnaire (n=522) and the ARSD initial caregiver questionnaire (n=244). Girls with a pathogenic *MECP2* mutation, who were 15 years or younger at the time of questionnaire completion, and whose parents provided the data of interest, were eligible for this study. The questionnaire asked caregivers about their daughter's best level of speech-language ability before and after speech-language regression with options being; no speech or language, babble, vocalisations with meaning, single words, two word combinations, three word combinations, and four or more word combinations. This

information was coded for analysis as one of the following mutually exclusive categories; no speech or language, use of babble or use of words.

Univariate linear regression was used to analyse the relationship between *MECP2* mutation type and the age of speech-language regression. Logistic regression was used to determine the relationship between *MECP2* mutation type and likelihood of experiencing a regression in speech-language abilities and multinominal logistic regression was used to examine the relationships between *MECP2* mutation type and the level of speech-language abilities.

The use of InterRett and ARSD provided a large sample size of 766 girls with Rett syndrome which would have unlikely been achieved using other recruitment methods. It also allowed diagnosis of Rett syndrome to be confirmed with available genetic data. All data cleaning, coding and analysis were carried out by the candidate in consultation with a statistician and the candidate's supervisors. The candidate completed the first draft of the publication. The candidate's supervisors reviewed drafts and provided feedback for consideration by the candidate.

3.3.3 Study 3 - An exploration of the use of eye gaze and gestures in females with Rett syndrome

The third study presented in this thesis also described the performance of producing communication and focused on the use of eye gaze and gestures, and the ability to make requests in 151 girls and women. Relationships between communication performance and genotype, gross motor abilities and age were also investigated. This study addresses relationships between impairment in body function and structure (genotype), personal factors (age) and activities (communication, mobility).

In 2004, 2007 and 2012, families who were part of ARSD were invited to complete an evaluation of their daughter's functional abilities, comprising two components: a video based filming protocol and a parent-report questionnaire termed the Functional Ability Checklist (FAC) (Fyfe et al., 2007). The filming protocol was broadly based on the domains of the Functional Independence Measure for Children (WeeFIM) (Msall et al., 1994) and asked parents to film their daughter performing a range of functional tasks (Fyfe, et al., 2007). The FAC asked parents to provide further detail on their daughter's functional abilities. This included 14 items from the Communication and Symboliv Behavior Scales Developmental Profile Infant-Toddler Checklist (CSBS DP ITC) (Wetherby & Prizant, 2002), as well as questions about gross motor abilities. Data from the most recently completed FAC was used to measure

communication performance, and video data from the same time point was used to measure gross motor performance.

Questions from the CSBS DP ITC (Wetherby & Prizant, 2002) were used in this study to gather information on communication abilities. The CSBS DP ITC is made up of 24 items asking parents to rate the frequency of communicative and symbolic behaviours on a three-point scale, “not yet”, “sometimes”, or “often”. The items form seven clusters measuring different abilities such as the expression of emotion and the use of eye gaze, and gestures. Cluster scores are generated by summing the scores of the individual items within that cluster (Wetherby & Prizant, 2002).

This study utilised data from 14 CSBS DP ITC items to outline the frequency with which girls and women expressed emotion and used eye gaze, used gestures and sounds, made requests and understood their name. Cluster scores for gestures and eye gaze were calculated. Higher scores indicated greater frequency of those behaviours (Wetherby & Prizant, 2002). Two requesting items from the “communication” cluster were used and each was coded into a binary variable, the girls and women who never or sometimes requested and those that often requested. To be eligible for this study, the girls and women had to have a pathogenic *MECP2* mutation and a FAC completed by a family member with no more than one missing communication item.

Gross motor abilities were measured using the video data collected at the same time as the FAC was completed (Fyfe, et al., 2007). Parents were asked to video their daughters completing a range of gross motor tasks based on items from the Gross Motor Function Measure (Palisano et al., 1997). Principal components analysis of the video data indicated two scales, a 10-item general gross motor scale and a 5-item complex gross motor scale (Downs, Bebbington, Jacoby, et al., 2008). The general gross motor scale included items such as the ability to sit on the floor, stand and take steps, and the complex motor scale included items such as ability to run and walk up and down slopes (Downs, Bebbington, Jacoby, et al., 2008). Items used in the current study were scored by two research assistants according to the level of assistance required to complete the task, ranging from a score of four for no assistance to a score of one for maximum assistance or being unable to complete the task, and summed to give a subscale score (Downs, Bebbington, Jacoby, et al., 2008). The measure has excellent inter-rater reliability (Foley, et al., 2011) and there is evidence for the measure's construct validity (Downs, Bebbington, Jacoby et al., 2008).

Pearson chi-square was used to compare the proportions of different *MECP2* mutation types in our sample to that of individuals registered with the ARSD but not included in our study. Multivariate linear regression was used to investigate relationships between age, *MECP2* mutation type and gross motor scores, and the outcomes of eye gaze and gestures scores. Analyses including gross motor scores were conducted for the subset of our sample who had a calculated gross motor score. Scores for the general gross motor subscale and complex gross motor subscale were coded as above or below the mean score for the sample to form two binary variables, one for each subscale. Univariate logistic regression was used to investigate the relationship between eye gaze and gestures scores, and females' ability to request help or an object, or attention. In this analysis, eye gaze and gestures scores were treated as continuous independent variables and the ability to request help or an object, or attention, were treated as binary dependent variables. This model also included an interaction between the eye gaze and gestures scores. For this analysis, to enable comparison with gestures scores, the eye gaze score was transformed to a score out of 10.

The ability to use data from the ARSD in this study allowed available communication data to be analysed with other available data on mobility, genetics and age. The use of video data to measure mobility strengthens this study as the video-based measuring system that was employed had excellent inter-rate reliability (Foley, et al., 2011) and there is evidence for the measure's construct validity (Downs, Bebbington, Jacoby et al., 2008). All data cleaning, coding and analysis were carried out by the candidate in consultation with a statistician and the candidate's supervisors. The candidate completed the first draft of the publication. The candidate's supervisors reviewed drafts and provided feedback for consideration by the candidate.

3.3.4 Study 4 - Choice making in Rett syndrome: A descriptive study using video data

The fourth and final study presented in this thesis utilised video data form the ARSD that was coded quantitatively to describe another aspect of producing communication, the ability to make choices. Relationships between the ability to make a choice and age, *MECP2* mutation type and functional abilities in 64 girls and women were explored in this study. Age was classified as a personal factor, *MECP2* mutation type an impairment in body function and structure, and functional abilities as activity limitations, respectively (World Health Organization., 2007).

Video data provided to the ARSD by caregivers of girls and women with Rett syndrome engaging in choice making interactions with familiar communication partners was used. Caregivers were instructed to show the girl/woman with Rett syndrome two objects, such as two items of food, and ask her to indicate her preference. Videos of choice making interactions were included in analysis if the girl/woman was instructed by a communication partner to make a choice between two or more different items and if the items and the girl/woman were visible for the duration of the interaction. If a girl or woman had more than one video meeting the inclusion criteria, each video was coded and the one demonstrating their best ability to make a choice was included in analysis.

A review of literature utilising video data to explore communication in girls and women with Rett syndrome was undertaken to identify a potential coding framework for the present study. The coding frameworks used in four studies were reviewed for the ability to code communication modalities and functions, including the ability to make a choice (Ryan et al., 2004 & Bartolotta & Remshifski 2013, Hetzroni, 2006; Bart-Pokorney 2013). These studies assessed different aspects of communication using different coding systems, of which none suited the purpose of this study. Therefore a coding framework was developed specifically for the purpose of this study. For example Bart-Pokorney and colleagues 2013 utilised the Inventory of Potential Communicative Acts (IPCA) (Sigafoos, Woodyatt, Keen, et al., 2000) to describe the communication modalities and forms used by infants prior to their diagnosis of Rett syndrome. However the IPCA lacks clear definitions of what constitutes the different communication modalities and forms. Our framework utilised the Communication Matrix (Rowland, 2004) to develop the definition of choice making and the modalities used to make a choice by girls and women with Rett syndrome and the modalities used by communication partners. This was chosen in preference to the IPCA (Sigafoos, Woodyatt, Keen, et al., 2000) as it had clear definitions for each communication function and modality that could be easily operationalised into codes.

The framework identified the location of the interaction, who the communication partner was, the number and description of choice items, the physical position of the girl/woman with Rett syndrome and whether the girl/woman made a choice. The communication modalities used were coded into categories based on The Communication Matrix (Rowland, 2004). Each video was coded by the candidate according to the coding framework outlined above. Additionally, a supervisor separately coded 15 videos to determine whether or not a choice was made to determine inter-rate reliability. The inter-rater reliability for coding the choice outcome was

calculated using Cohen's Kappa statistic (Cohen, 1960). Disagreements were resolved with discussion.

Age was calculated at the time the video was returned to the ARSD and the type of *MECP2* mutation was categorised using available data in the ARSD. The ability to walk and grasp objects was coded using video data from the same time point as the choice making interaction. Using follow-up questionnaire data, walking abilities were measured over time using up to six observation points. Using latent class group analysis a trend indicator that described the trajectory of walking was created and results in four distinct groups 1) always walked independently; 2) always walking with assistance; 3) deteriorating walking abilities and 4) always unable to walk (Downs, Torode, et al., 2016). Data on babbling and saying words at enrolment into the ARSD was obtained from responses to the question, "Which of the following best describes your child's use of speech at the present? No speech, babble, single words, 2 word sentences, 3 word sentences or 4 or more word sentences" in the initial questionnaire completed by families.

The characteristics of the sample and their choice making abilities were described. Fisher's exact test was also used to compare the proportion able to make a choice or not by age group, type of *MECP2* mutation, the ability to walk and grasp objects and speech-language ability at enrolment into the ARSD. The Kaplan-Meier method (Kaplan & Meier, 1985) was used to estimate the probability of making a choice, overall and by age group. The log-rank test was used to test the homogeneity of time-to-event functions across strata.

Use of the ARSD as the source of data of this study allowed data a large number of collected data, that was collected using a variety of methods, to be included and analysed. All coding of the video data and analysis were carried out by the candidate in consultation with the candidate's supervisors. Walking trajectory scores had been previously calculated by another member of the Australian Rett Syndrome Study team. The candidate completed the first draft of the publication. The candidate's supervisors reviewed drafts and provided feedback for consideration by the candidate.

Table 2. Summary of the methodology of each study including their objectives, design, data source and relevant ICF-CY chapters.

Study	Study objectives	Study design	Data source	ICF-CY domain(s)
Study 1	(1) Describe communication tasks including how girls and women communicate in everyday life according to parents (2) Describe relationships between a range of factors and communication performance including factors that parents believe are barriers or facilitators to successful communication.	Qualitative study	Transcripts of interviews with parents. For demographic information the initial and follow-up ARSD questionnaires for 15 females & the InterRett questionnaire for one female.	Activities & Participation: • Chapter 1 - Learning & applying knowledge • Chapter 3 - Communication • Chapter 4 - Mobility Body Functions & Structures: • Chapter 1 - Mental functions • Chapter 2 - Sensory functions & pain Environmental factors: • Chapter 1 - Products & technology • Chapter 3 - Support & relationships • Chapter 4 - Attitudes Personal factors
Study 2	(1) Describe communication tasks including the level of speech-language abilities before and after language regression (2) Describe relationships between a range of factors and communication performance including relationships between speech-language abilities and genotype	Quantitative cross-sectional study	Initial ARSD questionnaire & InterRett questionnaire	Activities & Participation: • Chapter 3 - Communication Body Functions & Structures: • Chapter 1 - Structures of the nervous system
Study 3	(1) Describe communication tasks including the use of eye gaze and gestures for requesting (2) Describe relationships between a range of factors and communication performance including relationships between genotype, age and motor abilities and the use of eye gaze and gestures	Quantitative cross-sectional study	ARSD initial questionnaire, ARSD FAC and ARSD video data	Activities & Participation • Chapter 3 - Communication • Chapter 4 - Mobility Body Functions & Structures • Chapter 1 - Structures of the nervous system Personal factors
Study 4	(1) Describe communication tasks including the ability to make choices (2) Describe relationships between a range of factors and communication performance	Quantitative cross-sectional study	ARSD video data & ARSD initial caregiver questionnaire and follow-up questionnaire	Activities & Participation • Chapter 3 - Communication • Chapter 4 - Mobility

	including relationships between genotype, age, the ability to walk and grasp, and speech language abilities and the ability to make choices			Body Functions & Structures • Chapter 1 - Structures of the nervous system Personal factors

Foreword to Chapter 4

The literature review identified a number of impairments in body function and structure, activity limitations and contextual factors that could impact on communication outcomes in girls and women with Rett syndrome. However information about parental perspectives on their daughter's communication abilities and the factors they believe may influence them has not been reported. The following chapter presents a qualitative study addressing two research questions from the perspective of parents (1) how do females with Rett syndrome communicate in everyday life? and (2) what factors act as barriers or facilitators to successful communication? Results from 16 interviews with parents are presented under the domains of the ICF-CY (World Health Organization, 2007). This study provides valuable depth to the findings of the quantitative studies presented in Chapters five to seven and is the first in-depth qualitative investigation of communication abilities in Rett syndrome.

This chapter is published in the journal Developmental Neurorehabilitation:

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Chapter 4: Parental perspectives on the communication abilities of their daughters with Rett syndrome

4.1 Abstract

This study describes, from the perspective of parents, how females with Rett syndrome communicate in everyday life and the barriers and facilitators to successful communication. Sixteen interviews were conducted with parents with a daughter with Rett syndrome with a pathogenic mutation in the *MECP2* gene. Interviews were recorded and transcribed verbatim. Transcripts were analysed using directed content analysis. All parents reported their daughters were able to express discomfort and pleasure, and make requests and choices using a variety of modalities including vocalisations, body movements and eye gaze. Parents also reported their daughters understood most of what they said and that the level of functional abilities, such as mobility, and environmental factors, such as characteristics of the communication partner, influenced successful communication. The perspectives of parents are integral to the assessment of communication abilities and have the potential to inform communication interventions for girls and women with Rett syndrome.

4.2 Introduction

Rett syndrome is a neurodevelopmental disorder affecting approximately 1 in 9000 Australian girls and women (Fehr, Bebbington, Nassar, et al., 2011) and is primarily caused by mutations in the X-linked *MECP2* gene (Amir et al., 1999). Girls and women with this disorder exhibit largely typical development in the first six to 12 months of life, followed by a period of regression during which language and hand function skills are lost and hand stereotypies develop (Neul et al., 2010). These language and motor impairments are often later accompanied by comorbidities such as seizures (Bao et al., 2013) and scoliosis (Ager et al., 2006). The severity of the clinical features of Rett syndrome varies between girls and women and is in part explained by their type of *MECP2* mutation. For example, girls and women with a p.Arg133Cys mutation tend to experience milder clinical features including later onset of regression and development of hand stereotypies (Bebbington et al., 2008).

The communication abilities of girls and women with Rett syndrome have been described using various methods including questionnaires (Bartolotta et al., 2011; Didden et al., 2010) and observations in structured contexts (Sigafoos, Laurie, & Pennell, 1995, 1996). Early descriptions of Rett syndrome highlight the use of eye gaze as a communication modality (Hagberg, 1995). Eye gaze is the most commonly reported modality used for expressive communication according to questionnaire data provided by parents (Bartolotta, et al., 2011; Didden, et al., 2010) and professionals such as teachers and speech-language pathologists (Bartolotta, et al., 2011). Body movements and communication devices such as picture boards are also commonly reported communication modalities, whereas use of words and sign language is less frequently reported (Bartolotta, et al., 2011). Other modalities, including laughing, smiling, crying and screaming, may also play communicative roles (Bartolotta, et al., 2011; Didden, et al., 2010). Girls and women with Rett syndrome use these modalities to fulfil a range of communicative functions such as making choices (Didden, et al., 2010; Sigafoos, et al., 1995) and requests (Didden, et al., 2010; Sigafoos, et al., 1996), and to answer, to reject and for social conventions (Didden, et al., 2010). The Inventory of Potential Communicative Acts (Sigafoos et al., 2000) was used by Didden and colleagues (2010) to describe the modalities used to fulfil 10 different communicative functions in 120 girls and women with Rett syndrome. As that is the only study to date to describe multiple modalities used for a range of communicative functions in girls and women with Rett syndrome, there is a need to replicate these findings. There is also a need to expand our knowledge on communication functions not specifically included in that study, such as showing affection, and on the composition of an individual girl's or woman's communication modality repertoire.

In terms of receptive communication abilities there is evidence that some girls and women with Rett syndrome can understand spoken words (Bartolotta, et al., 2011), match spoken words with their corresponding symbol (Baptista et al., 2006; Hetzroni et al., 2002), correctly identify concepts (Velloso et al., 2009) and match identical and similar pictures (Baptista, et al., 2006). Furthermore in terms of reading, the majority of respondents (parents, teachers and speech-language pathologists) to an online survey (n=141) were unsure if the female with Rett syndrome they cared for could read one or more single words (Bartolotta, et al., 2011). Yet in a sample of 13 girls and women with the ability to talk, six were reported to read at least a few single words (Kerr et al., 2006). Collectively these studies suggest that some girls and women can understand symbols, and spoken and written language but detailed descriptions of their ability to express that they have understood everyday communicative interactions is lacking, for example reacting appropriately when greeted by someone familiar or laughing appropriately at a joke.

The variability in communication abilities between girls and women with Rett syndrome is in part related to *MECP2* mutation type, level of functional abilities, epilepsy and the use of communication interventions. Girls and women with p.Arg133Cys mutations are more likely to use single words and phrases and those with a p.Arg270* or a p.Arg255* mutation are less likely to acquire the ability to speak (Bebbington, et al., 2008). Girls and women who speak may use a larger range of communication modalities (Bartolotta, et al., 2011) and be more likely to have the ability to read (Kerr, et al., 2006) in comparison to those who cannot speak. Communication abilities may also be influenced by the presence of apraxia (Bartolotta, et al., 2011) and other motor impairments (Cass et al., 2003; Fabio et al., 2009), epilepsy (Didden, et al., 2010; Vignoli et al., 2010), levels of attention (Fabio et al., 2011) and motivation which may be increased with music (Elefant & Wigram, 2005; Wigram & Lawrence, 2005) and food (Lavas, Slotte, Jochym-Nygren, van Doorn, & Witt-Engerstrom, 2006). Speech-language pathology (Bartolotta, et al., 2011) and communication interventions including the use of communication aids and devices (Koppenhaver, Erickson, Harris, et al., 2001; Sigafoos et al., 1996; Van Acker & Grant, 1995) and communication partner training (Bartolotta & Remshifski, 2013; Koppenhaver, Erickson, Harris, et al., 2001) may also play a vital role in the maintenance and development of communication abilities. Although a range of factors may influence communication abilities, no study to date has investigated all the possible factors that parents believe influence their daughter's communication abilities and nor has the influence of the full range of factors on communication abilities been investigated for Rett syndrome.

Parent report information, about the communication abilities of their children with severe physical and intellectual disabilities within the context of everyday life informs the prescription of appropriate communication interventions. Numerous studies have investigated parent perspectives on the communication abilities of their child with a disability including those diagnosed with Fragile X Syndrome (Brady, Skinner, Roberts, & Hennon, 2006), intellectual disability, Down syndrome, autism (Stephenson & Dowrick, 2005) and cerebral palsy (Deliberato & Manzini, 2012). Yet the literature for Rett syndrome does not provide a comprehensive description of the perspective of parents on the interplay between expressive and receptive communication abilities and the multiple factors influencing the communicative success of their daughters. Consequently the perspectives of parents, with a daughter with Rett syndrome, on their daughter's communication abilities should be explored. We therefore conducted a qualitative study using interviews with parents, with a daughter with Rett syndrome, to gain their perspectives on the following research questions: (1) How do females with Rett syndrome communicate in everyday life? (2) What factors act as barriers or facilitators to successful communication?

4.3 Methods

4.3.1 Procedure

The population-based ARSD database was established in 1993 and collects longitudinal information on Australian girls and women with Rett syndrome born since 1976 (Downs, Bebbington, Woodhead, et al., 2008). In 2011, 331 families caring for a girl or woman with a confirmed diagnosis of Rett syndrome were contributing to the database. Sixteen mothers, whose daughter had a pathogenic *MECP2* mutation and was living at home in 2011, were purposively selected to participate in this study based on the age of their daughter and her level of functional abilities as measured by the WeeFIM (Msall et al., 1994). This allowed us to describe a spectrum of communication abilities of girls and women with Rett syndrome across different ages and functional abilities. In total 15 mothers from the ARSD agreed to participate and the mother and father of an Australian woman born prior to 1976 and who was participating in the InterRett database (Fyfe et al., 2003; Louise et al., 2009) were recruited. Parents were provided with an information sheet outlining the purpose and procedures of the study, and given the opportunity to ask any questions of the researchers prior to completing an interview (Appendix B).

The ICF-CY (World Health Organization, 2007) informed the development of a semi-structured interview guide aimed at exploring communication abilities and the impairments, activity limitations and contextual factors that may influence these abilities (Power, Anderson, & Togher, 2011). The guide was piloted and adjusted according to feedback from three Australian mothers with a daughter with Rett syndrome who did not contribute data to this study (Appendix C). Interviews were recorded and transcribed verbatim by the first author. All participants received a copy of their interview transcript for checking and 12/16 provided feedback (Lincoln & Guba, 1985). This study was approved by the Edith Cowan University Human Research Ethics Committee (Appendix D) and pseudonyms have been used in this publication.

4.3.2 Data analysis

Interview transcripts were analysed using directed content analysis (Hsieh & Shannon, 2005). Guided by the ICF-CY (World Health Organization, 2007), we coded communication as expressive or receptive. The Communication Matrix (Rowland, 2004) was then used as a framework to code expressive communication abilities according to their modality and function. Finally, we explored the factors that parents felt influenced communication using the ICF-CY domains of body functions and structures, activities, environmental factors and personal factors as a framework (World Health Organization, 2007). After applying the initial coding framework, the data were reviewed to merge similar codes. Initial coding was completed by the first author and reviewed by two additional researchers to ensure the credibility of results. Any disagreements between researchers were resolved through discussion (Lincoln & Guba, 1985). NVivo 10 software (QRS International Pty Ltd, 2012) was used to manage and code transcripts.

4.4 Results

In total, 15 interviews with mothers and one interview with both parents were conducted ranging in duration from 15 to 66 minutes. Eleven were telephone interviews and five were face-to-face. The daughter with Rett syndrome was present at all face-to-face interviews. Descriptive characteristics of the girls and women with Rett syndrome are provided in Table 3. In the following sections, the results are presented in relation to the coding framework under the headings of expressive communication, receptive communication and factors influencing communication.

Table 3. Characteristics of the girls and women with Rett syndrome (n=16).

Girl/woman with Rett syndrome[a]	Age at interview (years)	Age when speech regressed (months)	*MECP2* mutation	Able to say single words at time of interview[b]	Level of assistance required to walk at time of interview	WeeFIM Score[c]
Sarah	2	13	p.Pro152Arg	No	Minimal	29
Rachel	3	Unknown	p.ArgR168*	Yes	Moderate	22
Rebecca	4	8	p.ArgR106Trp	No	Moderate	18
Sally	4	14	p.ArgR168*	Occasionally	Maximal	20
Tara	5	22	p.Arg270*	Yes	No assistance	35
Laura	6	18	C-terminal deletion	No	Maximal	19
Janet	6	18	p.ArgR168*	Occasionally	Maximal	36
Joanna	7	18	p.Arg255*	Yes	Moderate	21
Isabelle	11	Unknown	p.Arg255*	No	Maximal	21
Ashley	13	15	p.Arg133Cys	Yes	No assistance	43
Julia	14	18	p.Arg270*	Occasionally	Maximal	18
Cindy	16	24	C-terminal deletion	Occasionally	Minimal	59
Tegan	18	15	p.ArgR168*	No	Maximal	18
Jacinta	19	36	p.Arg133Cys	Yes	No assistance	63
Monica	29	15	p.ArgR168*	Yes	No assistance	30
Natalie	38	18	C-terminal deletion	Yes	No assistance	-

[a] Pseudonyms have been used; [b] Single words include word approximations, words recognised by parents only or conventional words; [c] Complete independence in daily activities such as mobility, feeding, dressing and communication is represented by the highest possible score of 126

4.4.1 Expressive communication

Multiple communication modalities are described along with their use in relation to expressing discomfort and protesting, choice making, requesting items and activities, requesting attention and socialising and expressing happiness.

4.4.1.1 Multimodal communication.

All parents reported that their daughter had a repertoire of modalities that could include body movements, gestures, eye gaze, vocalisation and production of words. The type and number of modalities used changed according to the context, for example a combination of leaning, eye gaze and/or vocalising was sometimes used when making choices. At times girls and women persisted with their communication, for example increasing the volume of vocalising until they were understood. Also one modality could have various functions for the same girl or woman, for example Joanna blew raspberries to indicate happiness and request attention. Girls and women, who were mobile or were able to speak, used more extensive repertoires than those with more limited functional abilities.

'With like her food… she will look and lean towards whichever she wants' (Sarah's mother).

'If she didn't want to watch it she would just vocalise… and then it would get intense and it would get louder as well' (Laura's mother).

4.4.1.2 Expressing discomfort and protesting.

The girls and women were usually able to indicate pain and feeling unwell, frustration and distress, toilet needs, fatigue, hunger and thirst. However, parents reported that understanding the exact cause of discomfort was usually challenging.

'*Deciphering whether she's trying to tell us something else or she's in pain, that's really hard to decipher, whether she has got pain or not*' (Julia's mother).

Body movements such as *'wriggling'* or *'fidgeting'* were used by girls and women without independent walking to communicate the need for a nappy change or the toilet, hunger or thirst. Specific body movements sometimes indicated localised pain, for example '*fisting, hands in the mouth all the time*' indicated toothache, which was confirmed by dental examination. Distress and frustration were sometimes indicated with facial expressions such as

a turned down and quivering bottom lip, faster breathing and *'more prominent'* hand stereotypies. Fatigue was expressed by closing or rubbing eyes or leaning on their parents. Distress and frustration, pain, hunger or thirst were also expressed with vocalisations including whinging and crying and some girls occasionally used symbols or words, for example, one girl said 'mama' when distressed and one woman sometimes said *'ou-ee'* to indicate pain.

Similar communication modalities were used as protests: body movements such as turning away or closing the mouth indicated disinterest in food during meal times; non-preferred people might be pushed or shoved away; and vocalisations indicated a protest when a preferred activity was finished. Two women used words to protest. One said *'no'* to protest against people trying to take away a present she had received at a Christmas party, and the other said *'toilet'* to get out of places when nervous. Parents also reported that protesting would cease if the situation was resolved.

'If I start to sing a song that she doesn't like she'll splash me or she'll… do high pitched squealing and scrunch up her face' (Joanna's mother).

4.4.1.3 Making choices.

All parents reported that their daughter was able to choose between at least two items such as movies, foods or drinks by using combinations of body movements, eye gaze, gestures and words. Eye gaze was most commonly used and was described as easy to interpret if *'intense'* and *'persistent'*. Eye gaze was sometimes used in conjunction with other modalities such as leaning and reaching towards their choice, symbols, words and finger pointing. Symbols included photos and pictures of food and drinks and one parent described their daughter as spelling out her choice on an alphabet board with physical assistance to support her wrist or elbow. Three of the girls and women communicated their choice with words such as *'yes'*, *'I want'* and the name of the chosen item, sometimes in conjunction with finger pointing and eye gaze.

'"What would you like for breakfast, would you like cereal or toast?" and we'd have the two objects there … "Use your eyes to make the choice, tell us what you'd like" and she'll look at the object, look back at us, look at the object and we'd say "Oh you'd like the cereal" and then she'll smile' (Janet's mother).

4.4.1.4 Requesting items and activities.

New items or activities were often requested with body movements and gestures. Examples included walking towards or pointing at a new item, or finding a new item around the home, such as a book, and bringing it to a family member. Girls and women who walked independently also walked to areas where food and drink was served to request foods or drinks and one girl used a sign for *'eat'*. One woman requested lipstick by pursing her lips when her mum was putting it on herself and one girl raised her arms to request to be picked up. Words and phrases were used by few girls and women to request items or activities. For example, Tara used single words such as *'milk', 'bottle'* and *'wiggles'* appropriately and Natalie used single words and phrases such as 'I want a cup of tea' and *'toilet'* appropriately, although the latter was also sometimes used to leave a non-preferred situation. Eye gaze was used frequently to request new items and activities when the girl or woman had the attention of their communication partner.

'*At meal times… if she's sick of eating and would like a drink, she'll just stop eating and look at the water and then look at me then look at the water and then look at me'* (Janet's mother).

More of an item or activity was also requested using body movements, vocalisations, including whinging, and eye gaze. Examples included repetitive *'hitting'* of the mouth or rubbing of fingers on the wheelchair tray to mean *'more food'*. A BIGmack switch with a pre-recorded message of *'more please Mum'* was used by one girl during meal times with some success and the Makaton sign for 'more' was used by two girls in different contexts; one during meal times and the other during singing interactions.

'She's addicted to her TV. If I was to turn that off I'd give her about 30 seconds and she would look at me as if to say, "Why did you do that?" and then she'd look back at the telly and it's not on and she would look at me, look at the telly, and look at me and then start to whinge as if to say, "Right, now turn it back on"' (Laura's mother).

4.4.1.5 Requesting attention & socialising.

Attention was requested using vocalisations including *'raspberries'* or *'screaming'*, body movements such as pulling people's hair or *'flicking things'* and sometimes with single words such as *'mum'* or *'dad'*. Most parents described their daughter as being *'interested in being with people'* and *'emotionally connected'*; examples of social interactions are presented in Figure 2. Girls and women expressed their interest and enjoyment in being with friends and

family by *'watching them'*, *'joining in'* on conversations, and smiling and laughing with others. Some girls and women displayed affection towards other family members with body movements such as touching them or stroking their face and when sitting in their lap, would *'cuddle'* and *'snuggle in'*. A three year old girl, Rachel, and 38 year old woman, Natalie, were able to use the word *'hello'* appropriately with verbal prompting most of the time. On one occasion Natalie said goodbye without prompting.

'[My husband's] dad was sitting on his front porch and he said "ta-ta Nat" and "ta-ta" is not really a word we use… she stopped and she turned around to look at him and she said "ta-ta poppy"' (Natalie's mother).

4.4.1.6 Expressing happiness.

Facial expressions such as smiles and grins; *'cheeky grin', 'big massive ear to ear grin',* and sounds, such as giggles, laughter and specific vocalisations including *'jibber jabber'*, calm sounds, and *'happy'* vocalising, were used to express happiness or excitement. Girls and women without independent walking expressed happiness with body movements such as *'dancing', 'shaking her upper torso'* and *'bobbing around'* and jumping, running and *'rushing'* around was used by those who walked independently. A few girls and women expressed happiness with blowing raspberries, happy cries and screams and one girl would sometimes hyperventilate when excited. Only one parent described their daughter using words to express excitement.

'She smiles, laughs, jumps around, runs around and she goes "Woo hoo", she does that a lot' (Jacinta's mother).

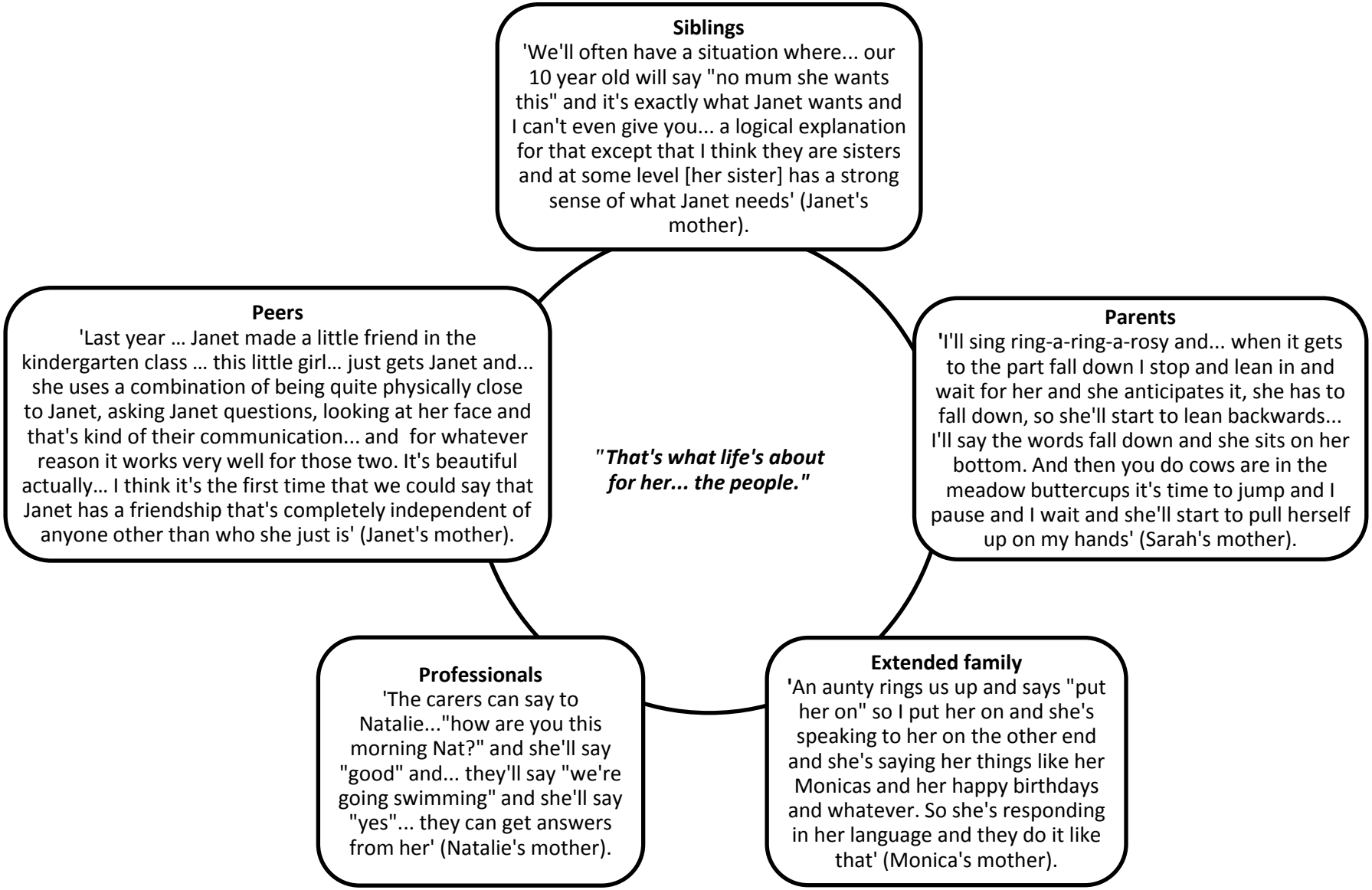
4.4.2 Receptive communication

The girls' and womens' abilities to understand the intentions of communication partners, when they use language and symbols, are described.

4.4.2.1 Understanding language.

Most parents believed their daughter could understand spoken language, stating their daughter *'understands everything quite well'*, while others described difficulties *'judging'* how much their daughter understood. Some parents felt that, if their daughter did not respond appropriately to an instruction, statement or question, it was not '*because of lack of understanding it's more because of the Rett syndrome, the ability to voluntarily do something.'*

Figure 2. Social interactions between the girls and women with Rett syndrome and their communication partners.



Most girls and women consistently responded to their name being called by looking and turning to the person who called their name and some responded appropriately to the name of other family members or pets, for example Laura got excited at the sound of her dog's name. Some parents also felt their daughter understood verbal instructions as evidenced by their ability to physically carry out instructions such as *'put your hand down'* and *'come on we're going to the shower'*. Some responded with appropriate body movements and eye gaze to statements such as *'tea's ready'* and questions such as *'where's daddy?'* During storybook reading, several girls responded with appropriate emotions and eye gaze to the story: *'she looks at the character… her eye gaze is appropriate to what the story is doing.'*

'The other day someone was looking after her… and this lady said to her… "we're going to go for a walk" and then she sat down and just finished her book and then Tegan got angry… she told her she was going for a walk and then she sat down and read her book and Tegan was mad like, "Why aren't we going for a walk?"' (Tegan's mother).

Most girls and women understood and answered yes/no questions using a variety of modalities including vocalisations, facial expressions, abstract symbols (touching yes/no cards), word approximations (*'ayeah'*) and single words (*'yes'*). Only one girl, Rachel, nodded and shook her head to indicate yes and no. Furthermore two women, Natalie and Monica, used language to answer questions; however, their answers were not always appropriate to the context, for example Monica sometimes answered a question inappropriately with *'happy birthday'*.

4.4.2.2 Understanding symbols.

Parents described their daughter's abilities to understand symbols such as Makaton signs, written words, photos and pictures. Some parents used Makaton signs in combination with language for *'more', 'stop', 'finished', 'drink'* and *'eat/food'*. Most parents were unsure or thought their daughter was unable to recognise her name or other written words, although one parent believed their daughter could *'read fine'*.

'At school… last year… they had to get up and pick their name off the board and she'd always find it with her eyes and then she'd get her head and touch it' (Tara's mother).

The girls and women demonstrated that they recognised people in photos '*with [their] eyes and… facial expressions'* and '*sometimes… a little giggle if there's somebody she… thinks is funny.'* The majority of parents believed their daughter responded more accurately to the

concrete representation of an item, like a photo, rather than a more abstract representation such as a picture or symbol. Additionally, one parent believed their daughter understood pictures better than spoken language, while another parent believed there was no difference between their daughter's ability to understand spoken language or pictures.

'We've found that she worked better with the actual photo rather than a stick… symbol' (Cindy's mother).

4.4.2.3 Factors influencing communication

Various factors were described as being facilitators or barriers to successful interaction with communication partners. These were coded using the ICF-CY (World Health Organization, 2007) concepts of body functions and structures, activities and contextual (personal and environmental) factors and are illustrated by sample quotes in Tables 4 and 5.

4.5 Discussion

Our findings demonstrate that parents believe their daughter with Rett syndrome is able to engage in meaningful interactions with communication partners with some understanding of language and symbols despite their language and motor impairments. However, reported communication abilities varied among the girls and women and there was variability also within each girl and woman. Influential factors included body functions and structures, activities and contextual issues. Some of the variation in communication abilities described in our sample may be explained by genotype (Bebbington, et al., 2008; Colvin et al., 2004) . For example, Jacinta's ability to use words to indicate pain, make choices and express excitement, can be explained in part by her p.Arg133Cys mutation which is associated with an increased likelihood of being able to talk in comparison to girls and women with other mutations (Bebbington, et al., 2008; Leonard et al., 2003). We also found that those who were able to speak used the largest repertoire of communication modalities, consistent with research in which respondents to an online survey (n=141) were likely to state that the female with Rett syndrome, who they cared for, used sign(s), pictures or symbols, gestures and/or body movements to communicate if she also spoke (Bartolotta, et al., 2011). Mobility, hand function and epilepsy, which have also been related to genotype (Bao, et al., 2013; Bebbington, et al., 2008; Colvin, et al., 2004), were reported to influence communication in our sample similar to previous research findings (Cass, et al., 2003; Didden, et al., 2010; Vignoli, et al., 2010). However, our results build on these findings as we also found that limitations in mobility and hand function restricted access to and use of some types of communication modalities and

Table 4. Body functions and structures, and activities influencing communication abilities.

ICF-CY domain	Sample quotes
Body functions & structures	
Psychomotor control	'*Some days obviously things will come out really easy and fluently and then other days there's … even up to a couple of minutes delay for her to be able to respond'* (Tara's mother).
Mood	*'Some days she really is in a bright happy mood and then [communication is] a lot easier… some days she's just very passive and quiet and then you don't get anything out of her'* (Tegan's mother).
Consciousness	*'I think it's if she's weary or tired she doesn't respond at all'* (Julia's mother).
	'If she's overtired … she'll just … shut down into a whinge or… her words are a lot easier to come and flow out a lot easier when she's in a really relaxed tired state' (Tara's mother).
Memory	*'You know if she hasn't seen somebody for 10 years she knows their name. And she'll call them by name'* (Natalie's father).
Sensory functions	*'If the environment's too busy … it's too much for her, that's when we sort of lose her, it's like she's got so much stimulation going in it's just … too much for her'* (Joanna's mother).
Activities	
Hand function	*'…she can't even point, she can't isolate an index finger … it's completely incumbent on the person that she's communicating with to be looking at her'* (Janet's mother).
Mobility	*'We'd chuck her on the trampoline and when you get her off it she'd just be like talking 10 to the dozen, well we couldn't understand what she said then but… any sort of exercise… it just sets her off'* (Natalie's mother).
	'She can't just go and walk to get what she wants. I think that makes it harder' (Rebecca's mother).
Learning	*'She's had the same teacher for three years and I think that's made a really big difference because she's been able to have the same program … and by having the same program and by having things constantly reinforced … it's definitely meant she's been able to move forward and improve her communication skills'* (Isabelle's mother).

Table 5. Contextual factors influencing communication abilities.

ICF-CY domain	Sample quotes
Personal factors	
Development	*'As they grow older, children develop… what she's going to do when she's 19 months old, what she's going to do when she's six [years] are totally different because her mental capacity and her ability to understand us is so much better'* (Laura's mother).
	'Before she got to puberty she was… full on talking, just "Blah blah blah"… When she hit puberty she started to slow down. Then she was stable for a little while and then she got a little bit slower and then she's been the same the last few years… she's definitely lost words. But she's still there' (Jacinta's mother).
Medical conditions	*'When she's having a lot of seizures… she gets very internally focused, like there's so much going on in her head that she doesn't respond to anything external at all'* (Isabelle's mother).
Environmental factors	
Music	*'She loves music… she can sing anything word to word on the radio. You put on a song and she'll sing it. It's always with something, she can't sing by herself but she'll sing word to word with what the bloke's singing. Some of the songs we've never heard of and she'd sing to them'* (Natalie's father).
	'She loves it when I sing to her and dance with her… that's when she gets real vocal' (Janet's mother).
Food	*'If it's food normally we'd get the response straight away… with other things it might take a bit longer'* (Ashley's mother).
Alternative and augmented communication	*'Our goal for this year is to try and become more informed about the PODD[a] system and work out if we're doing it the right way and to persevere with that'* (Janet's mother).
	'Facilitated communication … has it's plusses and it's downsides 'cause for it to be validated you need to be trained in facilitated communication so we've been lucky we've always had schools that have supported us and sent staff along to have them trained' (Cindy's mother).
Speech language pathology	*'I don't know if it actually improved her or whether she would of just gone through that whole sort of process on her own anyway'* (Tegan's mother).
	'The speech therapist he's put together her communication book and everything so it absolutely has made a difference to her communication' (Isabelle's mother).
Attitudes	*'The kids at school are great but often it's harder for the adults to accept facilitated communication'* (Cindy's mother).
	'I think that probably draws to… the wider issue of how people deal with… disability as a whole... I think often there's a temptation because Janet is little, to speak to her as if she's a baby' (Janet's mother).

ICF-CY domain	Sample quotes
Communication partner characteristics	
• Observing	*'I think the thing with Janet and the communication is I find her pretty easy to read because we have such … [an] intimate relationship but the thing I always … try and remind myself is I think Janet's easy to read because I spend a lot of time with her'* (Janet's mother).
• Waiting	*'It's about… being patient as well because she does get frustrated if people… ask her to do something and then wait two seconds… because she wants to do it and she'll get cross if we don't wait for her'* (Joanna's mother). *'It sort of sucks because everyone… really goes to her, no one holds back and gives her the time to go to them'* (Tara's mother).
• Establishing eye contact	*'She responds really well to people who get down at her level… the music teacher is really good with Sarah she does a lot … of one on one with her … so she stops and looks in Sarah's eyes and gets in her face and Sarah responds really well to that'* (Sarah's mother).
• Physical support	*'If you hold her left hand down… she has far better control over her right hand so she's able to actually reach out and … choose an item individually'* (Cindy's mother).

[a] PODD = Pragmatic Organisation Dynamic Display

that frequent seizures negatively influenced communication abilities and social interaction. Researchers and clinicians assessing the communication abilities of females with Rett syndrome should take the type of *MECP2* mutation into account in their assessment to help determine whether variations observed among girls and women are attributable to genotype.

In our study, modifiable environmental factors included activities and items perceived to be motivating for the girls and women and the characteristics of the communication partner. Parents identified music and food as increasing motivation and facilitating successful interactions with communication partners, confirming previous findings (Elefant & Wigram, 2005; Lavas, et al., 2006; Wigram & Lawrence, 2005). Similar to the findings of a survey of 141 individuals caring for a person with Rett syndrome, including parents, teachers and speech-language pathologists (Bartolotta, et al., 2011), only some of our parents felt speech-language pathology facilitated the development of communication abilities. Instead, skilful communication partners, who were able to establish eye contact, provide appropriate physical support, and, observe for and respond to communicative attempts within an appropriate time frame, were described as facilitating successful communicative interactions. Some of these

skills have been investigated in a study involving the training of four communication partners, of girls with Rett syndrome, and found similarly that skilled communication partners facilitated communicative interaction (Bartolotta & Remshifski, 2013). This emphasises the need for individualised communication assessment for girls and women with Rett syndrome that consider the influence of modifiable environmental factors that parents perceive to impact on communication abilities.

Our findings extend previous research by describing communication within the context of daily activities which has been infrequently described before (Didden et al., 2010; Woodyatt & Ozanne, 1992, 1993). Researchers have described the types of communication modalities used for different functions such as making requests (Didden, et al., 2010) and we were able to build on this information by describing how the girls and women often persisted with communication efforts until they were understood and that they may use the same modality, such as blowing raspberries, to serve more than one function. Interestingly, we found that the greatest range of modalities, from body movements and vocalisations to more complex abilities such as eye gaze and words, was used for requesting items and activities and making choices. This may be due to requesting and choice making being commonly viewed as a priority for communication intervention (Sigafoos, et al., 1995, 1996; Van Acker & Grant, 1995). Furthermore, parents in our study reported difficulties with determining the cause of pain in their daughters although most of the time they were able to identify when their daughter was in pain. Parents need to be able to identify when their daughter with Rett syndrome is in pain as they are primarily responsible for her care and comfort. However, girls and women with Rett syndrome may have a decreased sensitivity for pain and/or a delayed response to pain (Downs, Geranton, et al., 2010) and this may complicate interpretations of pain. Targeted communication interventions aimed at developing a consistent way for girls and women with Rett syndrome to express pain and the cause of pain should be considered.

Parents also believed their daughter could understand language regardless of her motor impairments, similar to previous reports by parents, teachers and speech-language pathologists (Bartolotta, et al., 2011). One of the challenges for future research is to validate parent report of receptive communication abilities within the context of everyday life using objective measures. Recent research suggests eye gaze technologies may be appropriate for this purpose (Djukic & McDermott, 2012; Djukic, McDermott, Mavrommatis, & Martins, 2012; Rose et al., 2013). Future research using this methodology should be expanded, ideally, by incorporating findings from this study, including collecting data on *MECP2* mutation type and functional abilities, to more accurately assess receptive communication in daily life.

The World Report on Disability recommended that the ICF (World Health Organization, 2001) be adopted universally to collect disability data (World Health Organization & The World Bank, 2011). This is the first study in the area of communication and Rett syndrome to use the ICF-CY (World Health Organization, 2007) to guide the collection and analysis of data. Our rich data set has allowed for an in-depth analysis of parental perceptions on communication abilities and the factors that influence successful communication. Furthermore our sample was purposively selected from the population-based ARSD Database and this allowed us to confirm the diagnosis of Rett syndrome with genetic data, which some previous studies have failed to do. However, we acknowledge that our findings may not be generalised to all girls and women with Rett syndrome due to the exploratory nature of the study and our small sample size. Furthermore there was variation in the length of each interview which may have influenced the amount of data provided; however, every parent was asked the same questions with opportunity to respond, and via member checking was able to provide additional information.

4.6 Conclusion

According to parents, girls and women with Rett syndrome are able to engage in meaningful interactions with their communication partners despite variability in expressive and receptive communication abilities. Assessment of communication needs to consider parental perspectives and factors that act as barriers or facilitators to successful communication, within the context of everyday life. Comprehensive assessment has the potential to facilitate successful interactions between girls and women and their communication partners. Clinicians and educators should also consider the possible adoption of the ICF-CY (World Health Organization, 2007) as a framework for assessment, to support engagement in meaningful social interactions and the prescription of appropriate communication interventions.

Foreword to Chapter 5

Chapters five to seven focus on examining relationships between different aspects of communication and impairments in body function and structure, activity limitations and contextual factors. This chapter presents a quantitative study describing the speech-language abilities of girls aged 15 years or younger and investigates the relationships between these abilities and *MECP2* mutation type. Upon diagnosis of Rett syndrome, caregivers are usually provided with genetic information. According to the ICF-CY (World Health Organization, 2007) a *MECP2* mutation can be considered an impairment in body function and structure. Caregiver questionnaire data from the ARSD and InterRett were used (n=766). This is the first study to solely focus on relationships between a range of speech-language abilities and *MECP2* mutation type in a large sample of girls with Rett syndrome.

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Chapter 5: Aspects of speech-language abilities are influenced by *MECP2* mutation type in girls with Rett syndrome

5.1 Abstract

This study investigates relationships between *MECP2* gene mutation type and speech-language abilities in girls with Rett syndrome. Cross-sectional data on 766 girls, aged 15 years and under, with genetically confirmed Rett syndrome was obtained from the ARSD (n= 244) and InterRett (n= 522). Relationships between *MECP2* mutation type and age of regression in speech-language abilities, and the level of speech-language abilities before and after this regression were investigated. The females had a median age of 4.95 years in the ARSD and 5.25 years in InterRett. The majority (89%, 685/766) acquired speech-language abilities in the form of babble or words at some point in time. Of those who acquired babble or words, 85% (581/685) experienced a regression in these abilities. Those with a p.Arg133Cys mutation were the most likely to use one or more words, prior to (RRR=3.45; 95% CI 1.15-10.41) and after (RRR=5.99; 95% CI 2.00-17.92), speech-language regression. Girls with Rett syndrome vary in their use of speech and language, and in their experience of speech-language regression and these variations are partly explained by genotype.

5.2 Introduction

Language is one of the most commonly used forms of communication for people of all ages but speech-language abilities are almost always serverely impaired in the neurodevelopmental disorder Rett syndrome. Rett syndrome is primarily caused by mutations in the X-linked *MECP2* gene (Amir et al., 1999). A period of developmental regression, during which spoken language and hand skills are partially or completely lost, is one of the essential criteria required for a diagnosis of typical Rett syndrome. Other essential criteria are the development of hand stereotypies and impaired mobility (Neul et al., 2010). Comorbidities including seizures (Bao et al., 2013), scoliosis (Ager et al., 2006) and breathing disturbances (Ramirez, Ward, & Neul, 2013) may also develop over time. There is considerable variability in the severity of these clinical features among affected girls and women (Bebbington et al., 2008), and as such there are also atypical presentations of Rett syndrome that do not always conform to the outlined typical criteria (Neul, et al., 2010).

The foundations of later speech-language abilities are established in the first year of life (Owens, 2012). Early development of speech and language involves the production of cries and pleasure sounds. Later, between four and nine months of age, typically developing children start to babble by producing combinations of consonant-vowel sounds (Sharma & Cockerill, 2014). They also start to understand spoken language prior to the development of more complex expressive language abilities, such as vocalisations with meaning and words (Owens, 2012; Sharma & Cockerill, 2014). Vocalisations with meaning, such as “da” for dad, usually develop between the ages of nine and 12 months and words commonly begin to emerge between 12 and 15 months (Sharma & Cockerill, 2014). Many girls and women with Rett syndrome learn to say words at some point in time (Bartolotta et al., 2011; Uchino, Suzuki, Hoshino, Nomura, & Segawa, 2001), although the development of speech-language abilities may be delayed and atypical (Marschik, Pini, et al., 2012; Tams-Little & Holdgrafer, 1996). The majority of girls and women experience a regression in speech and language abilities between 12 and 24 months of age (Bartolotta et al., 2011; Uchino et al., 2001). Following the regression period, only between 6% (20/331) (Kerr et al., 2006) and 18% (29/158) (Renieri et al., 2009) of girls and women have been reported to say words. Some have characterised this group as the preserved speech variant of Rett syndrome (Zappella et al., 1998). Little is known about other speech-language abilities, such as the ability to babble and vocalise (Marschik et al., 2013). These studies are the largest to date to specifically describe the use of and regression of speech-language abilities in Rett syndrome, but they have some methodological limitations in terms of the validation of diagnosis (Bartolotta, et al., 2011),

criteria used to describe language abilities (Kerr, et al., 2006; Renieri, et al., 2009; Uchino, et al., 2001) and population representativeness (Bartolotta, et al., 2011; Renieri, et al., 2009; Uchino, et al., 2001).

The successful development of speech and language is reliant on a number of genetic and environmental factors (Sharma & Cockerill, 2014). The *MECP2* gene is responsible for the production of the MeCP2 protein, which is important in the development and maintenance of the brain and nervous system (Cohen et al., 2011). Relationships between *MECP2* mutation type and general clinical severity, as well as specific features, have been identified in Rett syndrome (Bebbington, et al., 2008; Cuddapah et al., 2014; Neul et al., 2008). It is not known if MeCP2 plays a specific role in the development of speech-language abilities but some relationships between *MECP2* mutation type and speech-language abilities have been identified in Rett syndrome. For example, in an international study (n=276), girls and women with a p.Arg133Cys mutation were more likely to use single words and phrases, and those with a p.Arg270* or a p.Arg255* mutation less likely to acquire the ability to speak, compared to the overall sample (Bebbington, et al., 2008). Genotype also appears to influence the age at which girls experience developmental regression, with those with a p.Arg133Cys, p.Arg294* (Bebbington, et al., 2008) or C-terminal deletion (Fehr, Bebbington, Ellaway, et al., 2011) reported to regress later. However, it is still not known how genotype may influence other speech-language abilities such as babbling, and the timing of speech-language regression.

There remains the need to describe a range of speech-language abilities in a sample of girls with Rett syndrome large enough to fully investigate the effect of genotype, as the complete picture is unclear from the literature (Bartolotta, et al., 2011; Bebbington, et al., 2008; Cuddapah, et al., 2014; Kerr, et al., 2006; Neul, et al., 2008; Uchino, et al., 2001). We therefore conducted a study using a large sample of girls with Rett syndrome sourced from two databases, the population-based ARSD database (Downs, Bebbington, Woodhead, et al., 2008) and InterRett (Louise et al., 2009; Moore, Leonard, Fyfe, De Klerk, & Leonard, 2005), to describe a range of speech-language abilities and to investigate relationships with genotype.

5.3 Methods

5.3.1 Data management

Data from the ARSD and InterRett were used in this study. The ARSD was established in 1993 and continues to collect longitudinal data on Australian girls and women with Rett syndrome born since 1976 (Downs, Bebbington, Woodhead, et al., 2008). InterRett was established in 2002 and collects cross-sectional data on girls and women with Rett syndrome from 54 countries around the world (Louise, et al., 2009; Moore, et al., 2005). Upon enrolment into either database, questionnaires are completed by caregivers and/or clinicians who provide data on the early development, regression period and current functioning of the girl or woman with Rett syndrome. Girls with a pathogenic *MECP2* mutation, who were 15 years or younger at the time of questionnaire completion, and whose parents had provided data on regression in speech-language abilities, and the level of speech-language abilities before and after this regression, were eligible for this study. The age limit for eligible girls was restricted to 15 years and younger to minimise potential caregiver recall error (Majnemer & Rosenblatt, 1994; Russel, Miller, Ford, & Golding, 2013) but still capture those girls that may experience a late regression in speech-language abilities (Hagberg & Skjedal, 1994).

In terms of speech-language abilities, the questionnaire asked parents about their daughter's best level of ability before and after speech-language regression with options being; no speech or language, babble, vocalisations with meaning, singles words, two word combinations, three word combinations and, four or more word combinations. Using this information the level of speech-language abilities was coded for analysis as one of the following mutually exclusive categories; no speech or language, use of babble, or use of words. There was only a small number of girls able to combine words in our sample; 3.81% (22/577) of girls after experiencing an initial regression in speech-language abilities and 8.11% (15/185) of girls who did not experience speech-language regression. Therefore we combined girls able to use word combinations with those able to use vocalisations with meaning or single words in the 'use of words' category for analyses. Only those who acquired some form of speech or language could be coded as experiencing a regression in speech-language abilities. The type of *MECP2* mutations was categorised as one of the following: early truncation, large deletion, C-terminal deletion, p.Arg106Trp, p.Arg133Cys, p.Arg168*, p.Arg255*, p.Arg270*, p.Arg294*, p.Arg306Cys, p.Thr158Met or a group of other miscellaneous mutations.

5.3.2 Data analysis

Univariate linear regression was used to analyse the relationship between genotype and the age of speech-language regression. Logistic regression was used to determine the relationship between genotype and likelihood of reporting a regression in speech-language abilities and multinominal logistic regression was used to examine the relationships between genotype and the level of speech-language abilities. STATA software was used for statistical analyses (StataCorp LP, 2011). This study was approved by the Princess Margaret Hospital for Children (Appendix E and F) and the Edith Cowan University Human Research Ethics Committees (Appendix D).

5.4 Results

At the time of analysis the ARSD contained data on 244 eligible cases with a median age of 4.95 years (range 1.45-15.0 years) at ascertainment and InterRett contained data on 522 eligible cases with a median age of 5.25 years (range 1.16 years-14.95 years) at ascertainment. The most common point mutations were p.Thr158Met (11.75%, 90/766), p.Arg168* (10.18%, 78/766) and C-terminal deletions (9.65%, 74/766). The majority of girls, 89.43% (685/766), were reported to acquire some speech-language abilities in the form of babble or words at some point in time. Of the girls with some acquired babble or words, 84.82% (581/685) were reported to have experienced a regression in these abilities (Figure 3). The median age at this regression was 18 months (range 0.33-7.50 years) (n=495) and girls with a C-terminal deletion (RRR=5.80; 95% CI 0.92-10.65) or a p.Arg294* mutation (RRR=5.25; 95% CI 0.19-10.31) experienced a regression in speech-language abilities approximately five months after those with a large deletion (Figure 4). We did not find statistically significant relationships between *MECP2* mutation type and the likelihood of reporting a regression in speech-language abilities (Table 6).

The highest level of speech-language abilities acquired prior to experiencing a regression in speech or language was words for 77.43% (422/545) and babble for 22.57% (123/545). In comparison to girls with a large deletion, girls with a p.Arg133Cys mutation (RRR=3.45; 95% CI 1.15-10.41) were the most likely to be able to say words prior to speech regression (Table 7). After speech-language regression 21.49% (124/577) used words, 38.47% (222/577) were babbling and 40.03% (231/577) did not use babble or words. Of those girls able to use words after experiencing a regression in speech-language abilities, 17.74% (22/124) used words

Figure 3. Flow chart describing the speech-language abilities and regression in speech-language abilities in our sample (n=766).

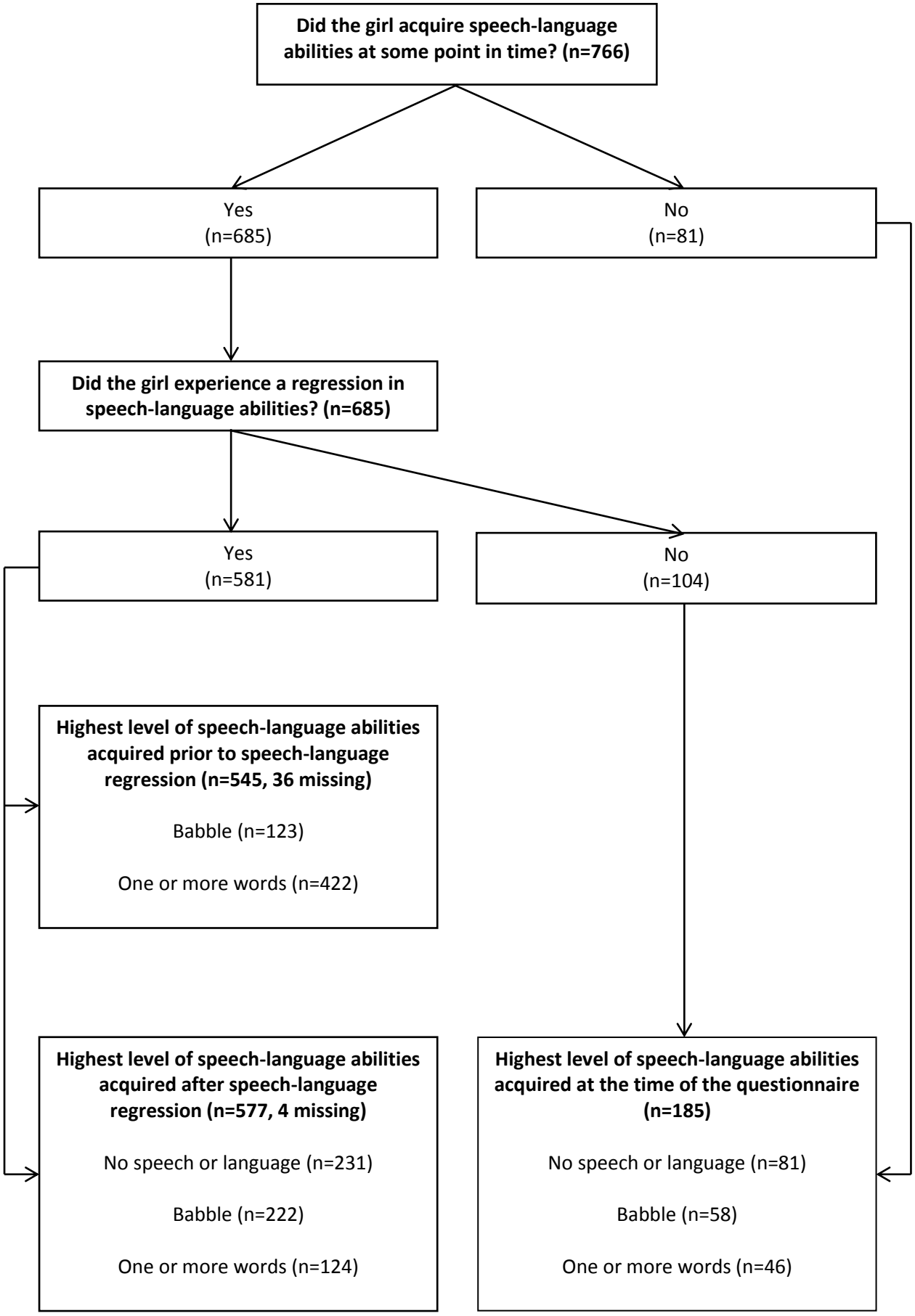

Figure 4. Adjusted mean age of regression of speech-language abilities (months) by type of mutation with 95% confidence intervals (n=495).

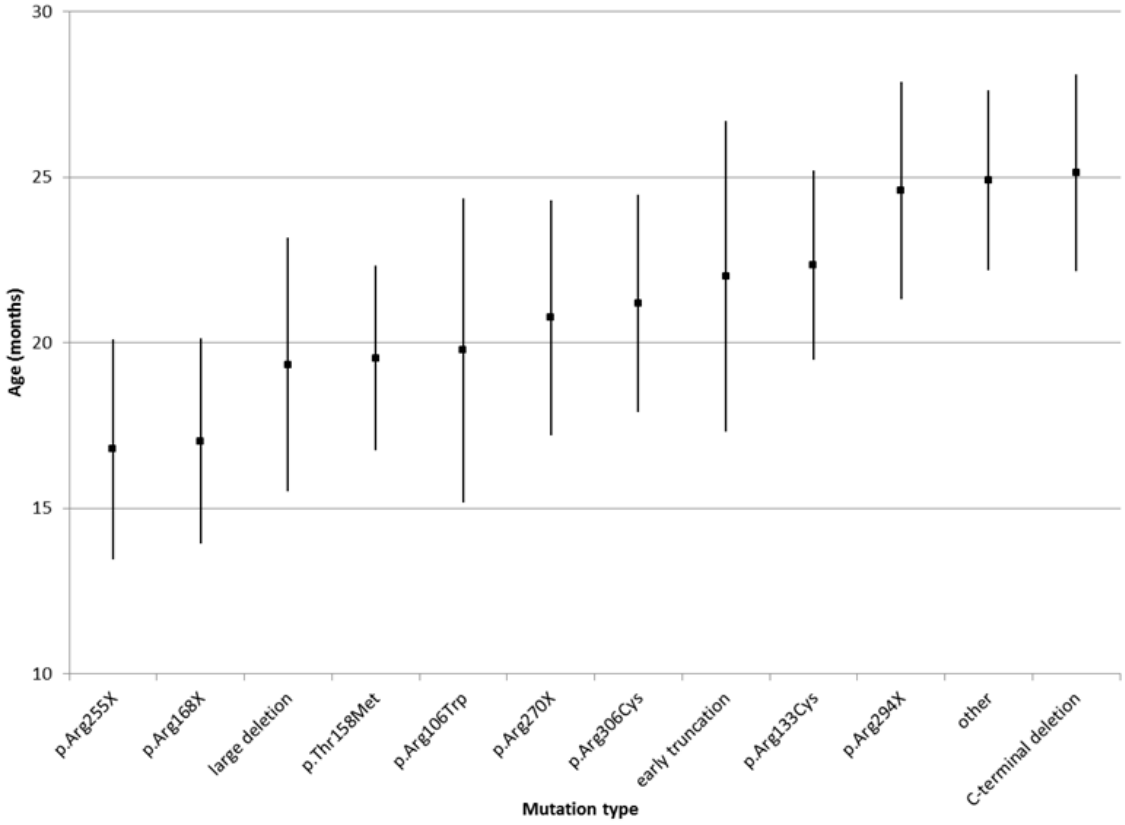

Table 6. Likelihood of experiencing a regression in speech-language abilities by type of mutation (n=766).

	Regression in speech	
Mutation type(n)	RRR (95% CI)	*p*-value
large deletion (53)	-	-
p.Arg106Trp (35)	0.94 (0.35-2.51)	0.90
p.Arg133Cys (63)	2.23 (0.85-5.90)	0.10
p.Arg168* (78)	0.65 (0.30-1.42)	0.28
p.Arg255* (67)	0.88 (0.39-2.02)	0.77
p.Arg270* (57)	0.83 (0.35-1.95)	0.67
p.Arg294* (61)	1.33 (0.55-3.23)	0.53
p.Arg306Cys (54)	2.18 (0.79-6.00)	0.13
p.Thr158Met (90)	0.95 (0.43-2.07)	0.89
C-terminal deletion (74)	0.94 (0.42-2.12)	0.88
early truncation (45)	0.49 (0.20-1.16)	0.10
other (89)	1.48 (0.65-3.39)	0.35

combinations, 13 combined two words, seven combined three words and two combined four or more words. Those with a p.Arg133Cys (RRR=5.99; 95% CI 2.00-17.92) remained the most likely to have the ability to say words after speech-language regression. Girls with a p.Arg168* mutation (RRR=3.43; 95% CI 1.10-10.70) or a p.Arg306Cys mutation (RRR=3.70; 95% CI 1.21-11.31) were also more likely to have the ability to say words after experiencing a regression in speech-language abilities in comparison to those with a large deletion. Girls with a p.Thr158Met mutation (RRR=4.76; 95% CI 1.87-12.10) or a p.Arg294* mutation (RRR=4.62; 95% CI 1.71-12.52) were the most likely to be babbling after speech-language regression (Table 7).

For those who did not experience a regression in speech-language abilities (n=185) the highest level of speech or language ever acquired was babble for 31.35% (58/185) and words for 24.87% (46/185), whilst 43.78% (81/185) never developed any speech or language. Of those girls able to use one or more words, 30.61% (15/46) used word combinations, one combined two words, six combined three words and eight combined four or more words. All mutations types were represented in the group of girls without a speech regression. The p.Arg255* (61.11%, 11/18) and p.Thr158Met (60.87%, 14/23) mutation groups had the highest proportion of girls without any speech or language, and the C-terminal deletion (57.89%, 11/19) and p.Arg133Cys (50.00%, 4/8) mutation groups had the highest proportion of girls with the ability to use words (Table 8).

5.5 Discussion

This study investigated speech-language abilities in one of the largest samples of girls with Rett syndrome to date. Accordingly, we have been able to explore variations in speech-language abilities among the girls and investigate relationships with genotype that were not previously possible. We found that the majority of the girls acquired babble or words at some point in time and that most, but not all, experienced a regression in these abilities. For those who did experience a speech-language regression, over two thirds used words before this regression but less than one fifth said words afterwards. The variation observed in speech-language abilities and age of speech-language regression was partly explained by genotype. Consistent with previous literature, individuals with mutations associated with milder presentations were more likely to use words before and after speech-language regression, and regress later than those with mutations associated with more severe presentations.

Table 7. Likelihood of speech-language abilities before and after experiencing a speech-language regression by type of *MECP2* mutation.

Mutation type (n)	Pre-regression level of speech-language abilities (n=545)		
	Babble	Words	
	Base outcome	RRR (95% CI)	*p*-value
large deletion (37)		-	-
p.Arg106Trp (24)		0.85 (0.28-2.55)	0.77
p.Arg133Cys (55)		3.45 (1.15-10.41)	0.03
p.Arg168* (48)		1.14 (0.44-2.94)	0.79
p.Arg255* (46)		0.87 (0.34-2.23)	0.78
p.Arg270* (39)		0.75 (0.29-1.98)	0.57
p.Arg294* (45)		3.38 (1.05-10.87)	0.04
p.Arg306Cys (44)		2.24 (0.76-6.53)	0.14
p.Thr158Met (63)		1.48 (0.59-3.72)	0.40
C-terminal deletion (53)		2.07 (0.76-5.65)	0.16
early truncation (24)		1.03 (0.33-3.17)	0.96
other (67)		1.60 (0.64-4.01)	0.31

Mutation type (n)	Post-regression level of speech-language abilities (n=577)				
	No speech or language	Babble		Words	
	Base outcome	RRR (95% CI)	*p*-value	RRR (95% CI)	*p*-value
large deletion (40)		-	-	-	-
p.Arg106Trp (25)		4.32 (1.39-13.40)	0.01	0.92 (0.16-5.45)	0.93
p.Arg133Cys (55)		2.78 (0.99-7.78)	0.05	5.99 (2.00-17.92)	0.001
p.Arg168* (52)		3.43 (1.27-9.28)	0.02	3.43 (1.10-10.70)	0.03
p.Arg255* (49)		2.22 (0.85-5.82)	0.10	0.67 (0.17-2.65)	0.56
p.Arg270* (41)		2.36 (0.87-6.41)	0.09	0.83 (0.21-3.36)	0.80
p.Arg294* (49)		4.62 (1.71-12.52)	0.003	2.50 (0.74-8.42)	0.14
p.Arg306Cys (47)		2.01 (0.71-5.70)	0.19	3.70 (1.21-11.31)	0.02
p.Thr158Met (66)		4.76 (1.87-12.10)	0.001	1.79 (0.55-5.84)	0.34
C-terminal deletion (55)		2.41 (0.91-6.37)	0.07	2.17 (0.70-6.74)	0.18
early truncation (26)		2.27 (0.71-7.28)	0.17	2.27 (0.60-8.64)	0.23
other (72)		1.97 (0.77-5.03)	0.16	2.55 (0.89-7.36)	0.08

Table 8. The level of speech-language abilities of girls who did not experience a speech-language regression by type of mutation (n=185).

Mutation (n)	Level of speech-language abilities		
	No speech or language n (%)	Babble n (%)	Words n (%)
large deletion (13)	7 (53.85%)	4 (30.77%)	2 (15.38%)
p.Arg106Trp (9)	5 (55.56%)	3 (33.33%)	1 (11.11%)
p.Arg133Cys (8)	3 (37.50%)	1 (12.50%)	4 (50.00%)
p.Arg168* (26)	13 (50.00%)	7 (26.92%)	6 (23.08%)
p.Arg255* (18)	11 (61.11%)	5 (27.78%)	2 (11.11%)
p.Arg270* (16)	6 (37.50%)	8 (50.00%)	2 (12.50%)
p.Arg294* (12)	6 (50.00%)	4 (33.33%)	2 (16.67%)
p.Arg306Cys (7)	1 (14.29%)	3 (42.86%)	3 (42.86%(
p.Thr158Met (23)	14 (60.87%)	6 (26.09%)	3 (13.04%)
C-terminal deletion (19)	4 (21.05%)	4 (21.05%)	11 (57.89%)
early truncation (18)	7 (38.89%)	6 (33.33%)	5 (27.78%)
other (16)	4 (25.00%)	7 (43.75%)	5 (31.25%)

A major strength of this study is the combined use of a population-based and an international data source providing information on over 700 girls with a diagnosis of Rett syndrome, confirmed with the presence of a pathogenic *MECP2* mutation. International databases such as InterRett (Louise, et al., 2009; Moore, et al., 2005) provide the capacity to investigate relationships between genotype and features of Rett syndrome as these analyses require a large sample size often not available otherwise (Leonard et al., 2013). This study has therefore been able to provide greater insights into the relationships between genotype and speech language abilities than previously documented (Bebbington, et al., 2008; Cuddapah, et al., 2014; Neul, et al., 2008). For example, it was already documented that individuals with a p.Arg133Cys mutation generally experience a milder presentation of Rett syndrome (Leonard et al., 2003) but we now also know that they experience speech-language regression later than those with other mutations. With the use of a large sample we have also been able to expand our knowledge of girls who are not well represented in the literature including those with less common *MECP2* mutations and those who did not experience a regression in speech-language abilities. For example, previous investigations have been limited in their capacity to provide insights into the relationships between the less common p.Arg106Trp mutation and clinical features of Rett syndrome due to including only nine (Neul, et al., 2008) or 18 females with this mutation (Bebbington, et al., 2008).

Studies utilising retrospective parent report have some inherent methodological limitations such as recall error (Ozonoff et al., 2011; Zwaigenbaum, Bryson, & Garon, 2013). However parent report questionnaires are useful in the study of large sample sizes with participants from varying geographical locations where it may not be feasible to use more direct methods for data collection such as video analysis (Leonard, et al., 2013). Some of our data was retrospective in that we asked parents about speech-language regression and their daughter's speech-language abilities prior to this regression, which usually occurs in the first few years of life (Lee, Leonard, Piek, & Downs, 2013; Neul et al., 2010). We minimised the potential for recall error by limiting the age of our sample to girls aged 15 years or younger at the time of questionnaire completion. We also asked parents about their daughter's speech-language abilities at the time of questionnaire completion and there is some evidence to support agreement between parent report data on current communication abilities and data reported by professionals (Bartolotta, et al., 2011) or collected from direct assessment (Eadie et al., 2010). Furthermore in our study parents did not have to complete every question in the questionnaire if they were unsure of the answer, as a result we have some missing data but the data we have collected may be more reliable. Another limitation is that our categories of speech-language abilities cannot distinguish variations in ability within each category. For

example those who have just begun to babble and those who may have more complex babbling would be categorised similarly. Factors that might account for variability in speech-language abilities within each mutation category, including epigenetic factors such as X-inactivation status (Archer et al., 2006) and environmental factors such as interventions targeting communication abilities (Bartolotta & Remshifski, 2013; Urbanowicz, Leonard, Girdler, Ciccone, & Downs, 2016), were not able to be investigated in this study. Furthermore in a small number of cases the questionnaire may have been completed prior to regression in speech-language abilities and thus we could have underestimated the proportion with a regression of speech-language abilities.

Generally, our results confirm previous investigations, each with their own strengths and limitations, which reported the ability to use words varied in Rett syndrome (Bartolotta et al., 2011; Kerr et al., 2006; Marschik et al., 2013; Uchino et al., 2001). In our study, 77% of girls said words prior to a regression in speech-language abilities. This is similar to the 70% reported to use meaningful words at some point in time from a survey of 141 parents, teachers and speech-language pathologists (Bartolotta, et al., 2011). Our results may be more accurate as the diagnosis of Rett syndrome was not confirmed in Bartolotta's (2011) survey and since their survey was completed anonymously, there could be duplicate entries on the same individual by different respondents. After language regression, 21% of our sample used words, similar to the proportion of 18% reported in a study using data from the British Isles Survey for Rett on girls and women aged over 10 years, with a pathogenic *MECP2* mutation (n=331) (Kerr, et al., 2006). From our study we can estimate that for girls who experience a regression in speech-language abilities, approximately three quarters will have the ability to say words prior to regression, but less than one fifth will continue to have this ability.

Our results largely confirmed reported relationships between genotype and aspects of phenotype. For example, in our study girls with the generally considered milder genotypes of p.Arg133Cys (Bebbington, et al., 2008; Leonard, et al., 2003; Neul, et al., 2008) and C-terminal deletion (Fehr, Bebbington, Ellaway, et al., 2011; Neul et al., 2008) were more likely to say words before and after speech-language regression, and regress later than those with a mutation associated with a more severe presentation. Interestingly, we found those with a p.Arg168* mutation, generally associated with a more severe presentation of Rett syndrome and the inability to say words (Neul, et al., 2008), to be more likely than those with a large deletion to be babbling or saying words after a speech-language regression. This is in keeping with a study that reported two out of 13 girls and women with meaningful speech after regression had a p.Arg168* mutation (Kerr, et al., 2006). Although some relationships between

genotype and overall clinical severity are well established (Bebbington, et al., 2008; Cuddapah, et al., 2014) and generally extend to our findings on speech-language abilities, we unexpectedly found some mutations usually associated with an overall more severe phenotype, such as p.Arg168* (Cuddapah, et al., 2014; Neul, et al., 2008), to be associated with less severely affected speech-language abilities.

A regression in spoken language is currently required for a diagnosis of typical Rett syndrome (Neul, et al., 2010), yet, similar to previous reports, not all of the girls in our investigation experienced such a regression (Bartolotta, et al., 2011; Uchino, et al., 2001). We also demonstrated that all types of common *MECP2* mutations were represented in those without a speech-language regression, although those with a C-terminal deletion (11/19, 57.89%) or a p.Arg133Cys (4/8, 50%) mutation made up the largest proportion of girls using words. This finding is similar to our results for the group of girls who did regress in speech-language abilities. Of the girls who did not regress in speech-language abilities, a quarter used words and clinically this group of girls may have been diagnosed with the atypical subtype of Rett syndrome, the persevered speech variant (PSV) (Neul, et al., 2010). Girls and women with speech after the developmental regression period were first described in the 1990s in a series of studies by Zappella (1992, 1994, 1997) and Zappella and colleagues (1998). They were described as a group that may possibly represent a unique subtype of Rett syndrome with different underlying aetiology to typical Rett syndrome (Zappella, 1992). Since this time there have been attempts at developing criteria for the PSV (Neul, et al., 2010; Renieri, et al., 2009) but these remain largely ambiguous and poorly adopted. Recent studies have used different criteria to define their cases as PSV (Marschik, Einspieler, Oberle, Laccone, & Prechtl, 2009; Marschik, Pini, et al., 2012) or have failed to clearly state the criteria they used (Marschik, Bartl-Pokorny, et al., 2014). Furthermore according to the current criteria for PSV it appears that girls who meet the typical criteria for Rett syndrome could be considered as PSV given that the major differential characteristic between these two groups is the presence of recovery of language after developmental regression (Neul, et al., 2008). With this in mind, and given that *MECP2* mutations are found commonly in those with typical Rett syndrome and PSV (Neul, et al., 2008), perhaps future research would benefit from considering Rett syndrome as a spectrum disorder with some individuals presenting with more severe features and some with milder features (Bebbington, et al., 2008; Cuddapah, et al., 2014; Neul, et al., 2008) rather than trying to define cases as PSV using criteria that at this stage remain largely unclear and inconsistently adopted.

Uncharacteristic presentations of Rett syndrome, including presenting with a late regression in spoken language, are associated with a delayed diagnosis (Fehr, Downs, Bebbington, & Leonard, 2010). Receiving a diagnosis is particularly important for families (Knott, Leonard, & Downs, 2011) and our results can inform clinicians about the variability of the experience of speech-language regression and of speech-language abilities in Rett syndrome. This knowledge, together with accurate assessment of speech-language abilities (Sigafoos et al., 2011) including early speech-language development (Budden, 2012) may facilitate the diagnosis of Rett syndrome in some cases. Findings can also be used to inform parents about clinical features that may be associated with their daughter's specific *MECP2* mutation and in the words of a mother with a daughter with Rett syndrome, give "insight into [their] future" (Knott et al., 2011). Future research can build on the knowledge available to clinicians and families by describing the speech-language abilities in Rett syndrome using more sensitive measures and as well as measuring speech-language abilities longitudinally. Furthermore in terms of extending our knowledge of the development of speech-language abilities it would be useful to compare the abilities of those girls with a regression in speech-language abilities to those who did not experience a speech-language regression as it is likely that such a regression would influence the trajectory of skill development.

Foreword to Chapter 6

Chapter six presents a quantitative study that used caregiver questionnaire data (n=151) from the ARSD to investigate the relationships between the use of eye gaze and gestures, and making requests in girls and women with Rett syndrome. This chapter incorporates the definitions of communication modalities presented in the Communication Matrix (Rowland, 2004). Eye gaze is defined in this chapter as visual form of communication including looking at a person or item and gestures are defined as conventional gestures including pointing to a person or item or nodding head 'yes' (Rowland, 2004). The influence of *MECP2* mutation type, gross motor abilities and age on the use of eye gaze and gestures was also investigated. This study addresses impairment in body function and structure, activity limitations and personal factors and is the first to investigate relationships between these domains of the ICF-CY (World Health Organization, 2007) and eye gaze and gestures in girls and women with Rett syndrome.

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Chapter 6: An exploration of the use of eye gaze and gestures in females with Rett syndrome

6.1 Abstract

This study investigates the communicative use of eye gaze and gestures in females with Rett syndrome. Data on 151 females with Rett syndrome participating in the ARSD was used in this study. Items from the Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist (CSBS DP ITC) (Wetherby & Prizant, 2002) were used to measure communication. Relationships between the use of eye gaze and gestures for communication were investigated using logistic regression. The influences of *MECP2* mutation type, age and level of motor abilities on the use of eye gaze and gestures were investigated using multivariate linear regression. Both eye gaze and the use of gestures predicted the ability to make requests. Women aged 19 years or older had the lowest scores for eye gaze. Females with better gross motor abilities had higher scores for the use of eye gaze and gestures. The use of eye gaze did not vary across mutation groups, but those with a C-terminal deletion had the highest scores for use of gestures. Eye gaze is used more frequently than gestures for communication and this is related to age, *MECP2* mutation type and gross motor abilities.

6.2 Introduction

Eye gaze and gestures are central to the development of language in children with and without developmental disabilities (Brady, Marquis, & Fleming, 2004; Watt, Wetherby, & Shumway, 2006). Furthermore, these abilities continue to serve communicative purposes in the presence of developed language in both these groups (Alamillo, Colletta, & Guidetti, 2013; Zampini & D'Odorico, 2009). Many children and adults with a severe developmental disability do not use spoken language as a form of communication and instead may rely on the use of eye gaze and gestures for communicative purposes, such as requesting (Bunning, Smith, Kennedy, & Greenham, 2013; Didden et al., 2009).

The neurodevelopmental disorder, Rett syndrome, is generally associated with intellectual disability, language and physical impairments, and comorbidities such as epilepsy (Bao et al., 2013) and scoliosis (Ager et al., 2006). The syndrome is primarily caused by a mutation in the *MECP2* gene located on the X-chromosome and therefore is seen almost exclusively in females (Amir et al., 1999). The *MECP2* gene encodes the protein MeCP2 which plays an important role in the development and maintenance of the nervous system (Cohen et al., 2011; Skene et al., 2010). Affected females predominantly develop typically until approximately 12 to 24 months of age, when a regression in hand and language abilities occurs, hand stereotypies such as wringing or clapping develop, and impaired mobility becomes apparent (Neul et al., 2010). The level of cognitive impairment in Rett syndrome is likely severe but rarely formally assessed due to the unique language and physical impairments associated with the syndrome, which prohibit use of conventional instruments (Byiers & Symons, 2012). On the whole, the severity of Rett syndrome can vary between individuals and is influenced by genotype (Bebbington et al., 2008; Cuddapah et al., 2014; Neul et al., 2008) and age (Cuddapah et al., 2014; Hagberg, 2002).

Rett syndrome is associated with severe limitations in the ability to use spoken language with only 21% (124/577) of girls in an international dataset aged 15 years and younger saying words post-regression (Urbanowicz, Downs, Girdler, Ciccone, & Leonard, 2014). Eye gaze, as a form of communication, is a supportive criterion for the diagnosis of atypical Rett syndrome (Neul, et al., 2010) and has been described as a communicative strength of girls and women with Rett syndrome (Hagberg, 1995; Urbanowicz et al., 2016). For instance, 79% (111/141) of respondents to a survey reported that the female with Rett syndrome they worked with or cared for used eye gaze for communication (Bartolotta et al., 2011). In another study of 120 parents, eye gaze was the most commonly reported form of communication used for social

convention, requesting an object or information, making a choice and answering (Didden et al., 2010). However, further objective information about the use of eye gaze and factors influencing its use is urgently needed.

There is limited information on the use of gestures by girls and women with Rett syndrome after the regression period; however, one survey of 141 parents and professionals found gestures were used by approximately 45% of females, less than the proportion who used eye gaze (Bartolotta, et al., 2011). Furthermore, an investigation using data from the Rett Syndrome Natural History Study reported just over half (286/542) of the girls learned to use gestures but only one in five of these retained this ability after regression (Neul et al., 2014). However, it is not clear if all the girls classified as retaining gestures also belonged to the group which had originally learnt this skill (Neul et al., 2014). The early development of a range of gestures, including finger pointing and showing an object, is often atypical in Rett syndrome (Marschik, Sigafoos, et al., 2012; Tams-Little & Holdgrafer, 1996). A retrospective parent-report study describing communication milestones in the girls' first 24 months reported five of 17 girls learned to use one gesture at a later age than would be expected and one girl attained gestures within typical age limits. The gestures outlined in the study included giving, pointing and showing gestures (Tams-Little & Holdgrafer, 1996). In a more recent video-analysis of seven girls with Rett syndrome, from the ages of 9 – 18 months, the number and types of gestures attained at an early age varied (Marschik, Sigafoos, et al., 2012). Research is required to understand the factors that may contribute to only a small proportion of girls and women using gestures after the regression period.

Personal factors such as genotype, gross motor ability and age may contribute to the variation observed in the ability to use eye gaze and gestures, as these factors have been reported to influence other communication abilities in girls and women with Rett syndrome. Genotype influences the severity of characteristics of Rett syndrome including language abilities, with those with a p.Arg133Cys mutation more likely to say words in comparison to those with other common mutations (Bebbington, et al., 2008). Those with a p.Arg133Cys mutation are also reported to have a less severe phenotype, experiencing better motor and hand abilities, which may also influence their ability to communicate (Leonard et al., 2003). The use of gestures for communication requires motor abilities that in Rett syndrome may be restricted by impaired motor skills associated with dyspraxia, a disorder of motor planning (Downs et al., 2014; Foley et al., 2011). Therefore, girls and women with better motor abilities may be more able to use gestures. With age, some girls experience deterioration in motor abilities, which might also impact the use of gestures (Hagberg, 2002), and women aged in their twenties or older

reportedly used eye gaze less frequently than younger girls and women to request an object (Didden, et al., 2010) and for general communicative purposes (Cass et al., 2003). However, these studies (Cass, et al., 2003; Didden, et al., 2010) only analysed univariate relationships between one factor and communication outcome, and did not account for interrelationships between factors. Therefore, there is a need for research investigating the multivariate relationships between communication abilities and multiple factors such as age, motor abilities and *MECP2* mutation type.

Requesting is one of the basic communicative functions required for social interactions and represents an important target for communication interventions in people with a severe developmental disability (Tait, Sigafoos, Woodyatt, O'Reilly, & Lancioni, 2004). Many girls and women with Rett syndrome are described by parents as “emotionally connected” and able to engage, with varying success, in interactions with a range of people (Urbanowicz et al., 2016, p. 20). According to parents, some girls and women are able to make requests for attention, objects, actions and information. However, the proportion able to do so has not been clearly reported (Didden, et al., 2010). Eye gaze is commonly reported to be used for requesting, while the use of gestures, such touching an object, is reported less frequently (Didden, et al., 2010). There is a lack of information on the use of gestures specifically for requesting and it is not known if eye gaze is more effective than gestures for communicative purposes such as making requests.

The influences of genotype, age and motor abilities on the use of eye gaze and gestures have not yet been explored in a large sample of girls and women with Rett syndrome. Furthermore, the impact of the use of eye gaze and gestures on the ability to make requests, an important communicative function, are unknown. This study aims to describe the relationships between the use of eye gaze and gestures and making requests, and understand how genotype, gross motor abilities and age influence these skills in girls and women with Rett syndrome.

6.3 Methods

6.3.1 Data source

This was a cross-sectional study using data provided by families participating in the ARSD. The ARSD is a longitudinal population-based database of Australian girls and women with Rett syndrome born since 1976 that uses a variety of methods, including questionnaires and video-based evaluations, to collect data about females and their families (Downs, Bebbington,

Woodhead, et al., 2008). Upon enrollment into the database, families complete an initial questionnaire about their daughter's early development, regression period and current functioning. This questionnaire includes questions about speech-language abilities (Urbanowicz et al., 2014).

In 2004, 2007 and 2012, families were invited to complete an evaluation of their daughter's functional abilities, comprising two components: a video based filming protocol and a parent-report questionnaire termed the Functional Ability Checklist (FAC) (Fyfe et al., 2007). The filming protocol was broadly based on the domains of the Functional Independence Measure for Children (WeeFIM) (Msall et al., 1994) and asked parents to film their daughter performing a range of functional tasks (Fyfe, et al., 2007). The FAC asked parents to provide further detail on their daughter's functional abilities. This included 14 items from the CSBS DP ITC (Wetherby & Prizant, 2002), as well as questions about gross motor abilities. Data from the most recently completed FAC was used to measure communication abilities, and video data from the same time point was used to measure gross motor abilities.

To be eligible for this study, the girls and women had to have a pathogenic *MECP2* mutation and a FAC completed by a family member with no more than one missing communication item. At the time of this study, the ARSD had information on 314 females with a pathogenic *MECP2* mutation, of whom 177 had a complete FAC. We excluded 26 females for whom a carer, rather than a family member, had completed the FAC leaving 151 girls and women meeting the inclusion criteria. We used data from 2012 for 100, from 2007 for 37, and from 2004 for 14 girls and women.

6.3.2 Communication variables

Data on babbling and speaking at enrollment into the ARSD was obtained from responses to the question "Which of the following best describes your child's use of speech at the present? No speech, babble, single words, 2 word sentences, 3 words sentences or 4 or more word sentences" in the initial questionnaire completed by families. This question was completed for 136 females meeting the study inclusion criteria. Questions from the CSBS DP ITC (Wetherby & Prizant, 2002) were used in this study to gather information on communication abilities. The CSBS DP ITC was designed for use with children aged six to 24 months to identify those who may have communication and other developmental delays (Wetherby & Prizant, 2002). It is made up of 24 items asking parents to rate the frequency of communicative and symbolic behaviours on a three-point scale, "not yet", "sometimes", or "often". The items form seven

clusters measuring different abilities including the expression of emotion and the use of eye gaze, and gestures. The “communication” cluster contains items asking about requesting help or an object, and attention. Cluster scores are generated by summing the scores of the individual items within that cluster (Wetherby & Prizant, 2002).

An early study of the validity and reliability of the CSBS DP ITC reported good test-retest reliability (ranging from 0.77-0.87) and moderate to high correlations (ranging from 0.40 – 0.74) between parent report CSBS DP ITC scores and scores derived from administration of the CSBS DP using direct observations in children with and without developmental concerns aged 12 - 24 months (Wetherby, Allen, Cleary, Kublin, & Goldstein, 2002). More recently a study of 728 Australian children aged 11.5 – 13.5 months found the overall concurrent validity between these two measures to be slighter lower but the gestures cluster had the highest agreement (r=0.41) between parent-report scores and scores calculated by professionals from direct observation (Eadie et al., 2010). These findings indicate that the CSBS DP ITC is appropriate for use in situations where the administration of the CSBS DP using direct observations is not feasible.

Due to the marked communication impairments associated with Rett syndrome, 14 items from the CSBS DP ITC were included in the FAC to gather information from parents about their daughter’s communication abilities. The use of CSBS DP ITC items to measure communication within the current study follows the assessment processes of previous investigations in which the communication abilities of children with a developmental disability, who are older than 24 months of age, have been assessed using tools designed for younger children (Maljaars, Noens, Jansen, Scholte, & van Berckelaer-Onnes, 2011; Roberts, Mirrett, Anderson, Burchinal, & Neebe, 2002). The CSBS DP ITC items used in the FAC were reworded to be appropriate for use with females with Rett syndrome of all ages, for example we used “your daughter” instead of “your child” (Fyfe, et al., 2007).

This study utilised data from 14 CSBS DP ITC items to outline the frequency with which girls and women expressed emotion and used eye gaze, used gestures and sounds, made requests and understood their name. Cluster scores for gestures and eye gaze were calculated. The gestures cluster comprised of five items and had a maximum total of ten points, and the three eye gaze items were summed to give a maximum total score of six points. Higher scores indicated greater frequency of those behaviours (Wetherby & Prizant, 2002). For individuals with only one missing gestures or eye gaze item, the missing item was imputed to generate a cluster score, by averaging the score of the other items in that cluster for that individual

(n=12). Two requesting items from the "communication" cluster were used and each was coded into a binary variable, the girls and women who never or sometimes requested and those that often requested.

6.3.3 Other variables

Age was calculated at the time the FAC was returned to the ARSD and categorised into the following groups; < 8 years, 8 < 13 years, 13 < 19 years and ≥ 19 years, representing the preschool and early school years, primary school years, adolescence and adulthood. The type of *MECP2* mutation was coded as one of the following: early truncation, large deletion, C-terminal deletion, p.Arg106Trp, p.Arg133Cys, p.Arg168*, p.Arg255*, p.Arg270*, p.Arg294*, p.Arg306Cys, p.Thr158Met or a group of other miscellaneous mutations.

Gross motor abilities were measured using the video data collected at the same time as the FAC was completed (Fyfe, et al., 2007). Parents were asked to video their daughters completing a range of gross motor tasks based on items from the Gross Motor Function Measure (Palisano et al., 1997). Principal components analysis of the video data indicated two scales, a 10-item general gross motor scale and a 5-item complex gross motor scale(Downs, Bebbington, Jacoby, et al., 2008). The general gross motor scale included items such as the ability to sit on the floor, stand and take steps, and the complex motor scale included items such as ability to run and walk up and down slopes (Downs, Bebbington, Jacoby, et al., 2008). Items used in the current study were scored by two research assistants according to the level of assistance required to complete the task, ranging from a score of four for no assistance to a score of one for maximum assistance or being unable to complete the task, and summed to give a subscale score (Downs, Bebbington, Jacoby, et al., 2008). Therefore, a score of 60 represents complete independence in all gross motor tasks and a score of 15 represents the need for maximum assistance or the inability to complete the task. On average, females with a score of 24 are able to sit independently but require moderate to maximal assistance with standing, transition and walking tasks and on average females with a score of 43 are able to sit, stand and walk independently but require assistance with transitions, running and walking on uneven or slopped surface. The measure has excellent inter-rater reliability (Foley, et al., 2011) and there is evidence for the measure's construct validity (Downs, Bebbington, Jacoby, et al., 2008). For the current study, a subset of 117 (77.48%) girls and women had calculated gross motor scores from video data. Thirty seven (31.62%) girls and women had three or fewer missing motor items from the video data so the FAC was used to provide the relevant item score.

6.3.4 Data analysis

Pearson chi-square was used to compare the proportions of different *MECP2* mutation types in our sample to that of individuals registered with the ARSD but not included in our study. Multivariate linear regression was used to investigate relationships between age, *MECP2* mutation type and gross motor scores, and the outcomes of eye gaze and gestures scores. Analyses including gross motor scores were conducted for the subset of our sample who had a calculated gross motor score. Scores for the general gross motor subscale and complex gross motor subscale were coded as above or below the mean score for the sample to form two binary variables, one for each subscale. Univariate logistic regression was used to investigate the relationship between eye gaze and gestures scores, and the girls' ability to request help or an object, or attention. In this analysis, eye gaze and gestures scores were treated as continuous independent variables and the ability to request help or an object, or attention, were treated as binary dependent variables. This model also included an interaction between the eye gaze and gestures scores. For this analysis, to enable comparison with gestures scores, the eye gaze score was transformed to a score out of 10. STATA software was used for analysis (StataCorp LP, 2011). This study was approved by the Princess Margaret Hospital for Children (Appendix E) and Edith Cowan University Human Research Ethics Committees (Appendix D).

6.4 Results

At enrollment into the ARSD the girls' highest level of speech-language abilities was one or more words for 16.18% (22/136), babbling for 55.88% (76/136) and 27.94% (38/136) did not say words or babble. At the time of the present study, ages ranged from 2.30 – 33.68 years with a median of 14.2 years. The most common mutations were p.ArgR168* (n=16), C-terminal deletions (n=16), p.Thr158Met (n=14), p.ArgR255* (n=13), p.Arg133Cys (n=12), large deletion (n=11), p.Arg270* (n=10) and p.Arg306Cys (n=10). The proportions of different *MECP2* mutation types in our sample (n=151) did not differ significantly from those in the ARSD who were not included in our study (n=149) (x2=9.706, p=0.557). The mean total gross motor score was 32.17 ± 14.81 (n=117). General gross motor scores ranged from 10 – 40 with a mean of 24.20 ± 11.31 and complex gross motor scores ranged from 5 – 20 with a mean of 7.97 ± 4.22.

The mean eye gaze score was 3.73 ± 1.40 (n=151) with scores ranging from zero to six. The majority of females often or sometimes engaged in the three eye gaze behaviours measured on the CSBS DP ITC. Eye gaze scores varied between girls and women of similar and different ages. This is illustrated in Figure 5 that shows individual eye gaze scores by age as a continuous

variable. When analysed according to age groups, those aged 8 < 13 years (coefficient 0.72, 95% CI 0.14 – 1.30) or 13 < 19 years (coefficient 0.87, 95% CI 0.24 – 1.50) used eye gaze more frequently than girls and women aged 19 years or older, after adjusting for *MECP2* mutation type (Table 9). Girls and women with better than average complex gross motor abilities (coefficient 0.68, 95% CI 0.06 – 1.30) used eye gaze more frequently than those with below average complex gross motor abilities, after adjusting for age and *MECP2* mutation type (Table 10). Mean eye gaze scores for the different *MECP2* mutation types ranged between 3.21 and 4.20 and these scores were not statistically different after adjusting for age (Table 9).

The mean gestures cluster score was 1.46 ± 1.96 (n=151) with scores ranging from zero to ten. Most females, regardless of age, did not use the gestures measured on the CSBS DP ITC at the time of this study. The results presented in Table 9 show the frequency of gesture use did not vary significantly across age groups and Figure 6 shows individual gestures scores by age as a continuous variable. On average, girls and women with a C-terminal deletion or a p.ArgR133Cys mutation used gestures with the greatest frequency. In comparison to those with a p.Arg168* mutation, those with a C-terminal deletion used gestures more frequently (coefficient 1.53, 95% CI 0.17 – 2.89). Girls and women with better than average general (coefficient 1.70, 95% CI 0.94– 2.47) or complex motor abilities (coefficient 2.25, 95% CI 1.49 – 3.00) reportedly used gestures more frequently than those with below average motor abilities, after adjusting for age and *MECP2* mutation type (Table 10).

One third (45/150) of girls and women were reported to let others often know that they needed help or wanted an object out of reach, with just under half (70/150) sometimes making this request. In relation to requesting the attention of others, 44.37% (67/151) often did this and 45.70% (69/151) sometimes did this (Table 11). Girls and women with higher eye gaze (OR 1.46, 95% CI 1.20 – 1.77) or gestures scores (OR 1.75, 95% CI 1.40 – 2.19) were more likely to request help or an object often. Similarly, those with higher eye gaze (OR 1.53, 95% CI 1.27 – 1.84) or gestures scores (OR 1.51, 95% CI 1.23 – 1.85) were more likely to request attention often. These results remained significant when eye gaze and gestures cluster scores were analysed together in a multivariate model (Table 11). There was no evidence of an interaction between the scores for the eye gaze and gestures cluster in predicting the ability to request help or an object (OR 1.03, 95% CI 0.90 – 1.18) or, attention (OR 0.92, 95% CI 0.82 – 1.02).

Figure 5. Eye gaze scores for individuals according to their age (n=151).

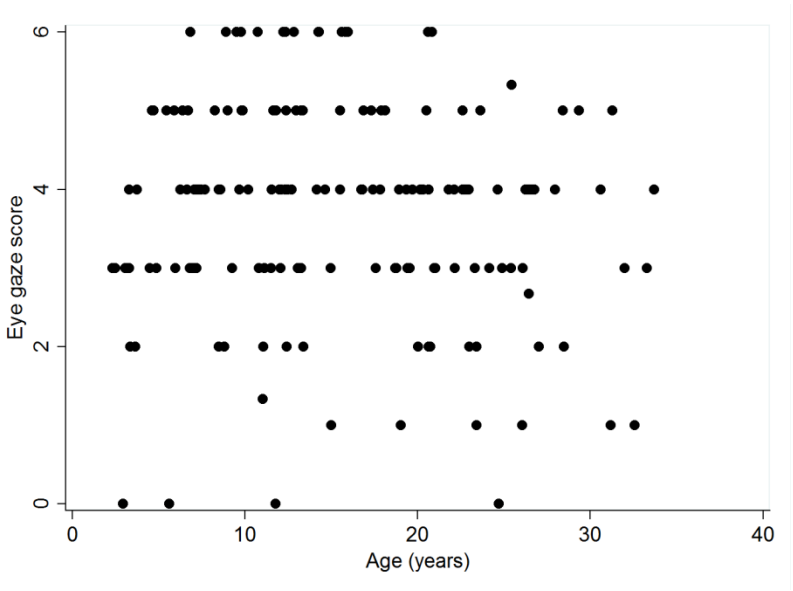


Figure 6. Gestures scores for individuals according to their age (n=151).

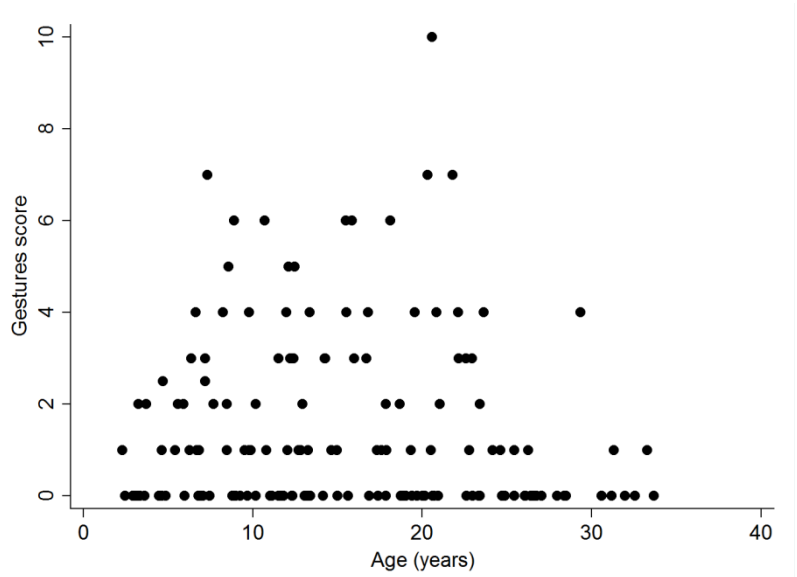


Table 9. Eye gaze and gestures scores according to age group and *MECP2* mutation type (n=151).

	Eye gaze			Gestures		
	Mean (SD)	Coefficient (95% CI)	*p*	Mean (SD)	Coefficient (95% CI)	*p*
Age group[a] (n)						
< 8 years (32)	3.56 (1.34)	0.22 (-0.38 – 0.83)	0.47	1.19 (1.57)	0.31 (-0.63 – 1.22)	0.50
8 < 13 years (37)	4.06 (1.49)	0.72 (0.14 – 1.30)	0.02	1.76 (1.95)	0.50 (-0.33 – 1.33)	0.23
13 < 19 years (29)	4.21 (1.26)	0.87 (0.24 – 1.50)	0.01	1.79 (2.01)	0.45 (-0.48 – 1.38)	0.34
≥ 19 years (53)	3.34 (1.35)	Baseline	-	1.24 (2.15)	Baseline	-
Mutation type[b] (n)						
p.ArgR168* (16)	3.69 (1.35)	Baseline	-	1.07 (1.66)	Baseline	-
large deletion (11)	3.30 (1.29)	-0.38 (-1.48 – 0.71)	0.49	1.21 (1.50)	0.14 (-1.36 -1.65)	0.85
p.ArgR106Trp (9)	3.44 (1.42)	-0.24 (-1.41 - 0.93)	0.68	0.33 (0.89)	-0.66 (-2.27 -0.94)	0.42
p.Arg133Cys (12)	3.92 (1.62)	0.23 (-0.84 - 1.30)	0.67	2.34 (2.15)	1.38 (-0.10 -2.86)	0.07
p.Arg255* (13)	4.08 (0.95)	0.39 (-0.66 - 1.44)	0.46	1.07 (1.38)	0.03 (-1.41 -1.48)	0.97
p.Arg270* (10)	4.20 (1.32)	0.51 (-0.62 - 1.64)	0.37	1.40 (1.84)	0.51 (-1.04 -2.05)	0.52
p.Arg294* (12)	4.17 (1.47)	0.48 (-0.59 - 1.64)	0.37	1.67 (1.84)	0.69 (-0.78 -2.17)	0.36
p.Arg306Cys (10)	3.63 (2.29)	-0.05 (-0.12 - 1.08)	0.92	1.50 (1.90)	0.25 (-1.30 -1.81)	0.75
p.Thr158Met (14)	3.21 (1.67)	-0.47 (-1.50 - 0.55)	0.36	0.81 (1.22)	-0.26 (-1.66 -1.14)	0.71
C-terminal deletion (16)	3.98 (1.12)	0.29 (-0.70 - 1.28)	0.58	2.53 (3.16)	1.53 (0.17 -2.89)	0.03
early truncation (7)	3.86 (0.69)	0.17 (-1.10 - 1.54)	0.79	0.44 (1.01)	-0.64 (-2.38 -1.09)	0.47
Other (21)	3.48 (1.33)	-0.21 (-1.14 – 0.72)	0.65	1.14 (1.71)	0.08 (-1.21 - 1.36)	0.91

[a] Analysis adjusted for mutation type; [b] Analysis adjusted for age

Table 10. Eye gaze and gestures scores according to gross motor abilities, adjusted for age and *MECP2* mutation type (n=117).

	Eye gaze			Gestures		
	Mean (SD)	Coefficient (95% CI)	*p*	Mean (SD)	Coefficient (95% CI)	*p*
General gross motor (n)						
Average & below (58)	3.47 (1.53)	Baseline	-	0.59 (1.14)	Baseline	-
Above average (59)	3.90 (1.42)	0.40 (-0.20 – 1.00)	0.188	2.37 (2.28)	1.70 (0.94 – 2.47)	<0.001
Complex gross motor (n)						
Average & below (74)	3.43 (1.49)	Baseline	-	0.69 (1.18)	Baseline	-
Above average (43)	4.12 (1.37)	0.68 (0.06 – 1.30)	0.033	2.86 (2.39)	2.25 (1.49 – 3.00)	<0.001

Table 11. The ability to request help or an object, and attention according to eye gaze and gestures scores.

	Requesting help or an object (n=150)			Requesting attention (n=151)		
	OR	(95% CI)	*p*	OR	(95% CI)	*p*
Eye gaze						
Unadjusted	1.46	(1.20 – 1.77)	<0.001	1.53	(1.27 – 1.84)	<0.001
Adjusted[a]	1.27	(1.03 – 1.56)	0.028	1.40	(1.16 – 1.71)	<0.001
Gestures						
Unadjusted	1.75	(1.40 – 2.19)	<0.001	1.51	(1.23 – 1.85)	<0.001
Adjusted[b]	1.60	(1.27 – 2.01)	<0.001	1.27	(1.02 – 1.58)	0.300

6.5 Discussion

In general, eye gaze was used more frequently than gestures, which is not unexpected give the motor impairments and dyspraxia usually associated with Rett syndrome (Downs, Bebbington, Jacoby, et al., 2008; Foley, et al., 2011). The use of eye gaze was found to vary with age, with those aged 19 years or older having the lowest reported scores for eye gaze. On average, girls and women with a *MECP2* mutation commonly associated with a milder phenotype, such as p.Arg133Cys (Leonard, et al., 2003; Neul, et al., 2008) or a C-terminal deletion (Bebbington, et al., 2008; Neul, et al., 2008), had more frequent use of gestures. About half of the girls and women were reported to consistently request attention and a smaller proportion were reported to request help or an object consistently. Those with higher eye gaze or gestures scores, representing more frequent use of these communicative behaviours, were more likely to be able to make requests than those with lower scores. To varying degrees, age, *MECP2* mutation type and gross motor abilities affected the frequency with which girls and women used eye gaze and gestures, and the frequency of the use of these skills affected their ability to make requests.

The girls and women in our study more frequently used eye gaze than gestures, providing further evidence for eye gaze abilities being a strength of the girls and women with Rett syndrome (Hagberg, 1995; Urbanowicz et al., 2016). More females in our study would often smile or laugh while looking at their parent/s than often look at their parent/s when playing with toys or other objects to see if they were watching or look at a toy or object if their parent/s pointed to it from across the room. This supports previous research where parents described their daughters as using smiles and laughter to express happiness (Urbanowicz et al., 2016), to socialise and make comments (Didden, et al., 2010). Looking at parent/s when playing with toys or other objects to see if they are watching, or looking at a toy or object if their parent/s pointed to it, represents more advanced eye gaze skills that are important for joint attention (Pence Turnbull & Justice, 2012). The low frequency of use of these behaviours suggests that cognitive abilities may be impaired. Poor joint attention skills may preclude some females from being able to utilise eye gaze technology (Djukic et al., 2012) which is being increasingly used to promote communication between girls and women with Rett syndrome and others. Therefore, intervention targeted towards improving joint attention skills will be important for some girls and women with Rett syndrome.

Motor abilities influenced both the use of eye gaze and gestures, but they had a greater effect on the ability to use gestures. This may help explain why fewer girls and women use gestures,

in comparison to eye gaze. Motor abilities are important for the use of gestures and may be impaired due to dyspraxia, which is viewed as a factor impacting the communication abilities of girls and women with Rett syndrome (Bartolotta et al., 2011; Woodyatt & Ozanne, 1994). However, many girls and women have been described in the literature as using body movements such as leaning and reaching to communicate (Bartolotta, et al., 2011; Didden, et al., 2010; Urbanowicz et al., 2016). These behaviours could be built into enhanced natural gestures that are more easily identifiable by others to allow them to communicate with more people (Calculator, 2002), and this may present an interesting opportunity for a future investigation. Enahanced natural gestures refers to intential motor behaviours that an individual already uses, or could be taught to use, to communicate without the need for physical contact with objects or people. For example an individual holding a cup and bringing it to their mouth may indicate a request for a drink, likewise the behaviour of moving their hand up to their mouth without a cup, could indicate a request for a drink (Calculator, 2002). This allows individuals with disability to communicate in everyday life without relying on the requested objects to be present.

Furthermore, having the ability to independently move and interact with the environment may contribute to the development of many cognitive abilities including those required to appropriately use gestures (Campos et al., 2000; Fischer & Zwaan, 2008; Longobardi, Spataro, & Rossi-Arnaud, 2014; Oudgenoeg-Paz, Volman, & Leseman, 2012; Wang, Lekhal, Aarø, & Schjølberg, 2014). As such, professionals involved in the provision of communication interventions for girls and women with Rett syndrome need to be aware of the possible impact motor abilities may have on their client's cognitive abilities and their ability to communicate. Opportunities to experience independent mobility and interact with the physical environment through play and other activities (Capone & McGregor, 2004) may be beneficial for the development of communication abilities in girls and women with Rett syndrome.

Girls and women younger than 19 years of age more frequently used eye gaze, when compared to those above this age. This is in keeping with previous investigations that found older women to use eye gaze for communicative purposes less frequently than younger girls (Cass, et al., 2003; Didden, et al., 2010). One explanation for this is that intervention is usually more available during the younger years, with research supporting the positive impact of early intervention on a range of skills in children with disability(Lai et al., 2014; van der Schuit, Segers, van Balkom, & Verhoeven, 2011; Ziviani, Feeney, Rodger, & Watter, 2010). Furthermore, older women may be presented with fewer opportunities to engage in communicative interactions. This will impact on their learning, and subsequently their ability

to continue to use certain communicative functions, such as eye gaze (Bartolotta & Remshifski, 2013; Elefant & Wigram, 2005). Older woman may also be living in residential settings, which have previously been reported to impact communication abilities in individuals with Rett syndrome (Didden, et al., 2010). Those living in residential settings have been shown to use a number of communicative forms, including eye gaze, less frequently than those living at home (Didden, et al., 2010). A similar trend was not observed with the use of gestures and age, possibly because the majority of females with Rett syndrome do not ever learn to use gestures. Opportunities to engage in communicative interactions should be encouraged into adulthood for those living with Rett syndrome to enable the continued reinforcement of learnt communicative behaviours, such as eye gaze. Furthermore there is a need to evaluate the relationship between pre-regression and later communication abilities to further understand the trajectory of the use of eye gaze and gestures.

Relationships between *MECP2* mutation type and the overall severity of Rett syndrome and language abilities are well recognised (Bebbington, et al., 2008; Cuddapah, et al., 2014; Neul, et al., 2008). Yet the influence of *MECP2* mutation type on other communication abilities, such as the use of gestures, has not been previously investigated. We found that those with a C-terminal deletion used gestures more frequently in comparison to girls and women with a p.Arg168* mutation. Given that C-terminal deletions are generally associated with less severe characteristics such as delayed onset of stereotypies and regression (Bebbington, et al., 2008) and retained hand function (Bebbington, et al., 2008; Neul, et al., 2008) this result is not entirely unexpected and may suggest that mutations associated with generally less severe phenotypes may also be associated with better communication abilities. This may be due to the effects of *MECP2* on other abilities important for functional communication such as motor abilities (Downs, Bebbington, Jacoby, et al., 2010; Fehr, Bebbington, Ellaway, et al., 2011; Foley et al., 2011). Encouragingly, we found the use of eye gaze did not differ across mutation groups, which may suggest that girls and women with a mutation that is generally associated with a severe phenotype such as a p.Arg168* or a p.Arg270* mutation (Bebbington, et al., 2008; Cuddapah, et al., 2014) use eye gaze for communicative purposes even if other communication abilities are impaired.

We found that less than half of girls and women with Rett syndrome often made requests for attention, for help or an object. In contrast, another study investigating communicative abilities in 120 girls and women with Rett syndrome reported that requesting was one of the "most often endorsed communicative functions" (Didden, et al., 2010, p. 110) but the exact proportion of girls and women able to do this was not presented. In our regression analysis we

grouped girls and women who “often” made requests separately to those who made requests “sometimes” or “never”. Therefore, our proportion of girls and women able to make requests represents those who have robust requesting abilities and not those with emerging or inconsistent abilities. This may explain the smaller proportion of girls and women reported to make requests in our study. Previous studies, with small sample sizes, provide some evidence for the ability of girls and women with Rett syndrome to learn to request objects (Sigafoos et al., 1996) (n=2) and activities (Elefant & Wigram, 2005) (n=1). The three girls in these studies predominantly used eye gaze to make requests, and we found an increased eye gaze or gestures score was associated with more frequent requesting. Although we found robust requesting to be infrequent in the girls and women, both the use of eye gaze and gestures, including enhanced natural gestures (Calculator, 2002), may be worthwhile targets for interventions teaching requesting (Keen, Sigafoos, & Woodyatt, 2001; Tait et al., 2004).

To date this is the largest study of the use of eye gaze and gestures, and requesting abilities of girls and women with Rett syndrome. It is also the first to use multivariate analysis to investigate the effect of factors on the use of eye gaze and gestures. Furthermore, this is the first study to use an overall scoring system to measure eye gaze and gestures and analyse relationships between scores and other factors such as age. We limited our sample to those with a pathogenic *MECP2* mutation to ensure a homogenous group. Furthermore, we restricted our sample to include only family reported data to reduce bias that might be introduced if data provided by carers, who may view the individual differently from their own family, was included (Julien, Parker-McGowan, Byiers, & Reichle, 2014). Additionally we included a range of ages in our study and the proportions of *MECP2* mutation types in our sample did not differ from those not included in our study but also registered with the ARSD. This suggests that our findings are representative of the population in terms of mutation type. The use of a valid and reliable parent-report measure of communication (Eadie et al., 2010; Wetherby et al., 2002) and a valid and reliable measure of gross motor abilities for use in Rett syndrome (Downs, Bebbington, Jacoby, et al., 2008; Foley, et al., 2011), adds strength to our conclusions.

However, our investigation does have limitations that need to be considered when interpreting our results. Although this is the largest study of its kind, the number of females within each mutation category may still have been too small to detect differences in the use of eye gaze. Also due to our sample size we may have not been able to detect an interaction between eye gaze and gestural abilities. We also did not include many other personal factors, such as epilepsy, that might influence communication in our analyses (Didden, et al., 2010).

Although the CSBS DP ITC may not provide the most robust measure of use of eye gaze and gestures specific to Rett syndrome, our study provides an opportunity for future investigations to validate our findings with different assessment procedures. Future investigations may benefit from using a variety of tools to gain a greater understanding of the use of eye gaze and gestures in different contexts and with a variety of communication partners (Woodyatt & Ozanne, 1993). One tool that should be considered is eye gaze technology (Baptista et al., 2006; Byiers & Symons, 2012; Djukic et al., 2012; Rose et al., 2013) that has the potential provide a more accurate measure of eye gaze than parent report through the CSBS DP ITC. As our study is cross sectional there is still a need for comprehensive longitudinal studies that investigate the impact of range of factors on communication.

6.6 Conclusions

This study demonstrated that girls and women with Rett syndrome frequently use eye gaze for communication despite often experiencing severe language impairments. Age, *MECP2* mutation type and the level of gross motor abilities were found to influence the use of eye gaze and gestures and these findings provide direction for professionals regarding factors that may need to be considered during communication assessment and intervention. Due to the relationship between motor abilities and communication, a multidisciplinary approach considering the contributions of speech-language pathology, physiotherapy and occupational therapy could be beneficial for girls and women with Rett syndrome. Interventions aimed at the development of eye gaze and gestures, and training communication partners to recognise, accurately interpret and appropriately respond to these methods of communication may be beneficial. Our findings also provide a foundation for future investigations into the barriers and facilitators of successful communication between girls and women with Rett syndrome and other people. Furthermore, studies are required to determine if communication assessment and intervention, which take into account the factors we identified, are beneficial for girls and women with Rett syndrome and their families in terms of the provision of appropriate planning and interventions for communication abilities.

Foreword to Chapter 7

Chapter seven describes the choice making abilities of girls and women with Rett syndrome and the relationships between these abilities and the girl's or women's age, *MECP2* mutation type and functional abilities. These factors are classified as a personal factor, an impairment in body function and structure and activity limitations respectively (World Health Organization., 2007). This study uses video data provided to the ARSD by caregivers of girls and women with Rett syndrome engaging in choice making interactions with familiar communication partners (n=64). This is the first study to use video data to investigate choice making abilities and to quantify the length of time required to make a choice by girls and women with Rett syndrome.

This chapter is currently under review in the journal Disability and Rehabilitation.

Chapter 7: Choice making in Rett syndrome: A descriptive study using video data

7.1 Abstract

This study describes the choice making abilities of girls and women with Rett syndrome. Females with Rett syndrome registered with the ARSD with a pathogenic *MECP2* mutation were included in this study. Video clips showing choice making in 64 females at a median age of 11.6 years (range 2.3 – 35.6 years) were analysed. Video clips were coded for the location and nature of the choice making interaction, and the actions of the communication partner and female with Rett syndrome. The majority (82.8%, 53/64) of females made a choice, most using eye gaze. Just under half (24/53) used one modality to communicate their choice, 52.8% used two modalities and one used three modalities. Of those who made a choice, 50% did so within 8 seconds. The length of time to make a choice did not appear to vary with age. During choice making, 57.8% (37/64) of communication partners used language and gestures, 39.1% (25/64) used only language and two used language, gestures and symbols within the interaction. The provision of adequate time allowing for a response and observation for the use of multiple modalities could promote effective choice making in females with Rett syndrome.

7.2 Introduction

Rett syndrome is a neurodevelopmental disorder caused by mutations in the X-linked *MECP2* gene and seen mainly in females (Amir et al., 1999). Development in Rett syndrome appears to be largely typical prior to the occurrence of a period of regression during which hand stereotypies develop and impaired language and motor abilities become apparent. These impairments are often severe and remain present to varying degrees throughout the lifespan (Neul et al., 2010).

The majority of females with Rett syndrome experience difficulties with communication (Cass et al., 2003; Didden et al., 2010; Urbanowicz et al., 2016) and only small proportions use words (Urbanowicz et al., 2014) or gestures for communication (Didden et al., 2010). More commonly, affected females use eye gaze (Bartolotta et al., 2011; Didden et al., 2010) which has been recognised as a communicative strength of girls and women with Rett syndrome since the early 1990s (Hagberg, 1995) and is considered a supportive feature for a diagnosis (Hagberg et al., 2002; Neul et al., 2010). Body movements and communication devices including picture boards are also used by some females for communication (Bartolotta et al., 2011).

Providing females with Rett syndrome with opportunities to communicate their needs and desires has the potential to positively influence their participation in everyday life (Walker et al., 2014). Therefore is it not surprising that choice making has been described as the most commonly targeted communicative function by speech language pathologists (SLPs) working with individuals with Rett syndrome (Wandin et al., 2015) and the most common reason for using eye gaze technology with individuals with Rett syndrome (Townend, Marschik, et al., 2015). Two UK studies, one using multidisciplinary clinical assessment (Cass et al., 2003) and the other a questionnaire completed by caregivers (Cianfaglione et al., 2015) , reported that 51.2% (43/84) and 67.0% (61/91) of females with Rett syndrome were able to make a choice, respectively. Studies with smaller sample sizes provide some further insight into choice making abilities. Results from a study that specifically assessed choice making in seven girls (Sigafoos et al., 1995) as well as those from our own interview study with 17 parents (Urbanowicz et al., 2016) demonstrated that females with Rett syndrome had the ability to make a choice, even if they did not do this consistently (Sigafoos et al., 1995; Urbanowicz et al., 2016). Girls and women with Rett syndrome may also be able to learn to make choices using augmentative and alternative communication methods according to small sample studies involving three (Stasolla et al., 2015), four (Sigafoos et al., 1996) and seven females (Elefant & Wigram, 2005).

Despite the importance of choice making, the current literature does not provide a detailed description of choice making abilities of girls and women with Rett syndrome. Nor does the literature adequately describe the relationships between choice making and factors known to influence other communication abilities such as *MECP2* mutation type (Urbanowicz et al., 2014) and the context of the communicative interaction (Hetzroni & Rubin, 2006; Ryan et al., 2004). We therefore conducted this study to describe the choice making abilities of girls and women with Rett syndrome and the factors that may influence their ability to make a choice using video data available in the ARSD (Fyfe et al., 2007).

7.3 Methods

7.3.1 Participants

Participants for this study were sampled from the population-based ARSD Database, established in 1993. The ARSD uses a variety of methods, including video, to collect longitudinal data on Australian girls and women with Rett syndrome born since 1976 (Fyfe et al., 2007). Upon enrolment into the database, families complete an initial questionnaire about the early development, regression period and current functioning of the girl or woman with Rett syndrome. This questionnaire includes questions about speech-language abilities (Urbanowicz et al., 2014). Additionally, since the year 2000 families have completed a follow-up questionnaire approximately every two years. This questionnaire includes questions about medical conditions and care, specific Rett syndrome behaviours, the use of resources such as therapy and everyday functioning including walking ability.

In 2004, 2007 and 2012 families registered with the database were invited to provide information on their daughter's functional abilities, using two tools: a video based filming protocol and a parent-report questionnaire (Fyfe et al., 2007). The filming protocol was broadly based on the domains of the WeeFIM (Msall et al., 1994) and asked parents to film their daughter performing a range of functional tasks, including a choice-making activity (Fyfe et al., 2007). Video clips of choice-making of girls and women with a pathogenic *MECP2* mutation were included in this study.

7.3.2 Procedure

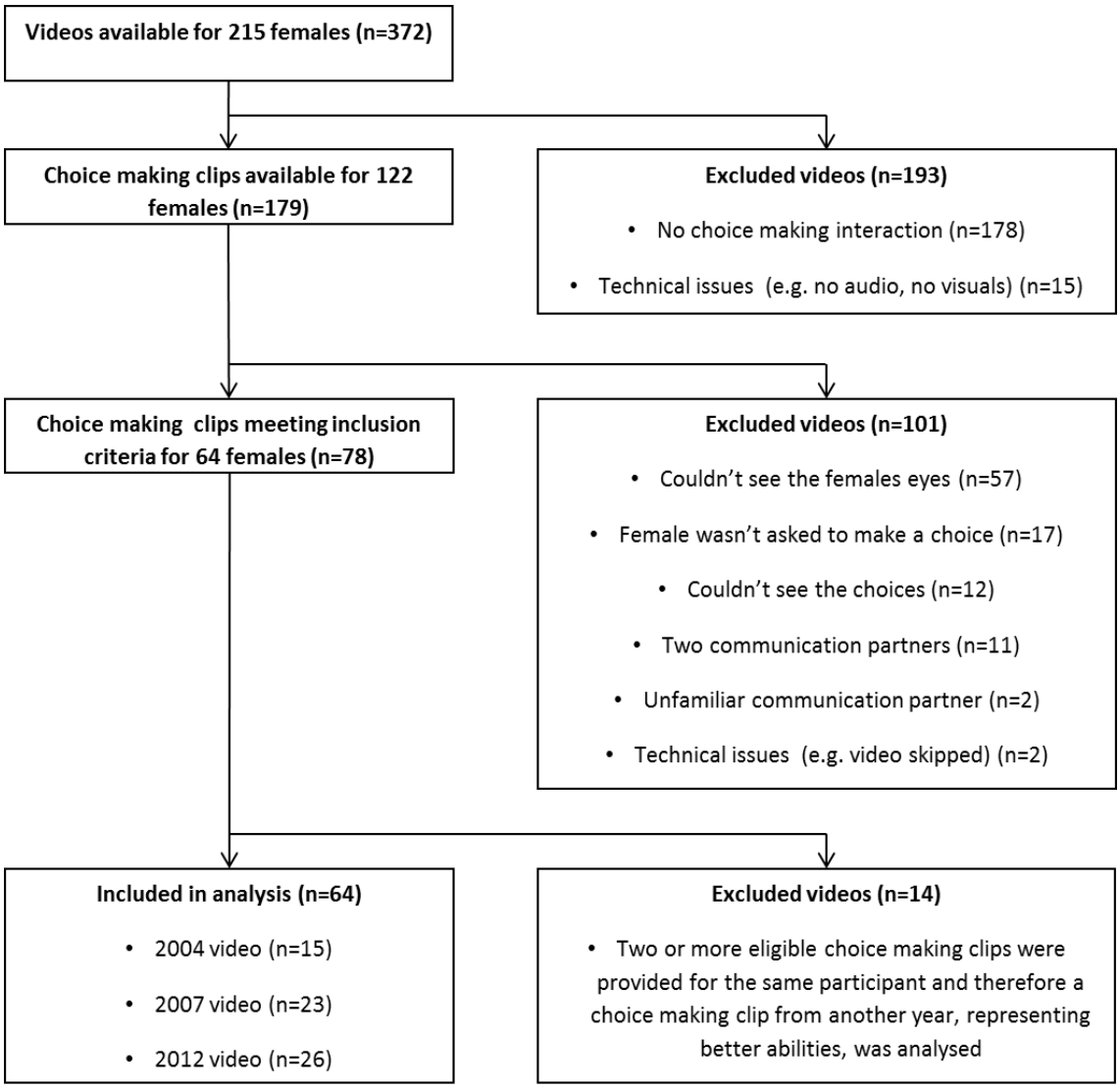
The video based filming protocol instructed parents/caregivers to show the girl/woman with Rett syndrome two objects, such as two items of food, and ask her to indicate her preference. Videos were screened for inclusion and included if the girl/woman was instructed by a communication partner to make a choice between two or more different items and that the items and the girl/woman were visible for the duration of the interaction. The video also needed to be of satisfactory quality so the interaction could be clearly seen and heard. If a girl or woman had more than one video meeting the inclusion criteria (i.e. a video had been provided in multiple years), each video was coded and the one demonstrating their best ability to make a choice was included in this study. Videos where the girl/woman made a choice were included in favour of videos where she did not, and videos with a faster time to choice were included in preference to those with a slower time to choice.

In total, 372 videos across the three time points were available for 215 girls and women. Of these videos, 179 included a choice making interaction for 122 girls and women and 78 videos met the inclusion criteria for the choice making interaction as outlined above. Fourteen videos were excluded from analysis as the parent/caregiver had provided another video of a choice making interaction representing better abilities. Therefore 64 videos of choice making interactions, representing 64 females with Rett syndrome, were analysed in this study (Figure 7).

7.3.2.1 Video coding

A coding framework was developed specifically for the purpose of this study that identified: the location of the interaction, for example at the participant's home; who the communication partner was, for example a parent or a staff member; the number and description of choice items; the physical position of the girl/woman with Rett syndrome, whether the girl/woman made a choice and how long it took. The communication modalities used by the communication partner and the girl/woman with Rett syndrome were coded into categories based on The Communication Matrix (Rowland, 2004), an evidence-based assessment tool of expressive communication of people with severe and multiple disabilities (Rowland, 2011). This included information about looking and detailed whether the girl or woman looked at the item and back at the communication partner.

Figure 7. Flowchart of the selection of videos for inclusion.



or after the communication partner used prompts they were coded as making a choice with prompts.

Initially the ability to make a choice was coded into one of three categories; able to make an independent choice, able to make a choice with prompts and not able to make a choice. If the girl or woman indicated her choice following the communication partner's initial instruction without any repeat of instruction or additional prompts such as pointing to the items, she was coded as making an independent choice. If the girl or woman indicated her choice after a repeat of the instruction.

The coding framework was piloted by the first two authors with nine videos. There was a high level of agreement in relation to the majority of elements of the coding framework however the definition of the choice making outcome was changed from three categories, as described above, to two categories; choice and no choice. The modification was made as some

communication partners used prompts when they presented the choice making scenario, such as pointing at the choice items as they labelled them, therefore the distinction between the ability to make an independent choice and a choice with prompts was not clear (Appendix G).

All videos were coded according to the outlined framework by the first author. The coding included verbal and nonverbal forms of communication used by the girl/woman or communication partners. The length of time taken to make a choice (seconds) was also determined by measuring the time between the communication partner ending the first verbal instruction and the girl/woman indicating her choice.

7.3.2.2 Inter-Rater Reliability

The first two authors seperately coded 15 videos to determine whether or not a choice was made. The inter-rater reliability for coding the choice outcome between the first and second author were calculated using Cohen's Kappa statistic (Cohen, 1960). A kappa coefficient above 0.8 was interpreted as excellent, 0.6 – 0.8 as substantial, 0.4 – 0.6 as moderate and below 0.4 as poor (Portney & Watkins, 2009). The kappa coefficient was 0.7 (95% CI 0.19 – 1.15) indicating substantial reliability.

7.3.3 Other variables

Age was calculated at the time the video was returned to the ARSD and categorised into the following groups; < 8 years, 8 < 13 years, 13 < 19 years and ≥ 19 years representing the preschool and early school years, primary school years, adolescence and adulthood. The type of *MECP2* mutation was coded as one of the following: early truncation, large deletion, C-terminal deletion, p.Arg106Trp, p.Arg133Cys, p.Arg168*, p.Arg255*, p.Arg270*, p.Arg294*, p.Arg306Cys, p.Thr158Met or a group of other miscellaneous mutations. The ability to walk and to grasp objects was coded using video data from the same time point as the choice making interaction. The ability to walk was coded in one of the following three categories: able to walk 10 steps independently, able to walk 10 steps with minimal or moderate assistance, or able to walk 10 steps with maximal assistance or unable to walk (Downs, Bebbington, Jacoby, et al., 2008). The ability to grasp objects was coded in a binary fashion independent if the girl/woman was able to grasp and pick up an object of any size unable to grasp if they required assistance or were not able to grasp (Downs, Bebbington, Kaufmann, et al., 2010). Using follow-up questionnaire data, we also measured walking abilities over time using up to six observation points. In each follow-up questionnaire walking was categorised as walking independently, able to walk with assistance or unable to walk. Using latent class group analysis

a trend indicator that described the trajectory of walking was created and resulted in four distinct groups 1) always walked independently; 2) always walked with assistance; 3) deteriorating walking abilities and 4) always was unable to walk (Downs, Torode, et al., 2016). Data on babbling and saying words at enrolment into the ARSD was obtained from responses to the question, "Which of the following best describes your child's use of speech at the present? No speech, babble, single words, 2 word sentences, 3 word sentences or 4 or more word sentences" in the initial questionnaire completed by families.

7.3.4 Data analysis

Chi squared and Fisher's exact test was used to compare the proportions of different *MECP2* mutation types and walking trajectory of our sample to that of individuals registered with the ARSD not in our study. Descriptive statistics were used to describe the characteristics of our sample and their choice making interactions. Fisher's exact test was also used to compare the proportion able to make a choice or not by age group, type of *MECP2* mutation, the ability to walk and grasp objects and speech-language ability at enrolment into the ARSD.

The Kaplan-Meier method (Kaplan & Meier, 1985) was used to estimate the probability of making a choice, overall and by age group. The log-rank test was used to test the homogeneity of time-to-event functions across strata. All analyses were conducted using STATA 12 (StataCorp LP, 2011). This study was approved by the Princess Margaret Hospital for Children (Appendix E) and Edith Cowan University Human Research Ethics Committees (Appendix D).

7.4 Results

At the time of the video, the 64 females were aged 2.30 – 35.64 years with a median age of 11.65 years. The most common mutation in our sample was p.Arg270* (14.06%, 9/64) and p.ThrT158Met (11.44%, 27/236) was the most common mutation in those in the ARSD not included in our study (Table 12). Overtime, 46.03% (29/63) of girls/women always walked independently in comparison to 34.27% (73/213) of girls/women in the ARSD not included in our study. The proportions of different *MECP2* mutation types (n=64) and walking trajectories (n=63) in our sample did not differ significantly from the proportion of different *MECP2* mutation types (n=236, p=0.43) and walking trajectories (n=213, p=0.24) in the ARSD who were not included in our study.

The characteristics of the sample and their ability to make a choice are presented in Table 13. The majority (82.81%, 53/64) of our sample made a choice between two or more items. For

Table 12. Proportion of *MECP2* mutation types and walking trajectories of our sample (n=64) and those in the ARSD not included in this study (n=236).

Characteristic	Our sample n (%)	Those in the ARSD not included in this study n (%)	*p*-value[a]
Mutation type			
p.Arg106Trp	3 (4.69%)	11 (4.66%)	
p.Arg133Cys	6 (9.38%)	17 (7.20%)	
p.Arg168*	6 (9.38%)	26 (11.02%)	
p.Arg255*	6 (9.38%	11 (4.66%)	
p.Arg270*	9 (14.06%)	19 (8.05%)	
p.Arg294*	6 (9.38%)	18 (7.63%)	
p.Arg306Cys	5 (7.81%)	13 (5.51%)	
p.Thr158Met	4 (6.25%(	27 (11.44%)	
C-terminal deletion	6 (9.38%)	22 (9.32%)	
Early truncation	1 (1.56%)	22 (9.32%)	
Large deletion	4 (6.25%)	18 (7.63%)	
Other	8 (12.50%)	32 (13.56%)	0.43
Walking trajectory[b]			
Always walked independently	29 (46.03%)	73 (34.27%)	
Always walked with assistance	8 (12.70%)	33 (15.49%)	
Deteriorating walking abilities	11 (17.46%)	32 (15.02%)	
Always unable to walk	15 (23.81%)	75 (35.21%)	0.24

[a] Fisher's exact test was used to compare the proportion of mutation types between groups and chi square was used to compare the proportion of walking trajectory categeries; [b] Walking trajectory data available for 63/64 cases in our sample and for 213/236 cases in the ARSD not included in this study

those who made a choice (n=53) the length in time it took to make a choice ranged from 1 second to 4 minutes 6 seconds with a mean of 14.47 ± 33.57 seconds. Females of different age groups, *MECP2* mutation types, walking and grasping ability and speech-language ability at enrolment into the ARSD were able to make a choice. The proportion able to make a choice did not appear to vary according to age group, *MECP2* mutation type, the ability to walk or grasp or speech language ability at enrolment into the ARSD (Table 13).

Videos were filmed at home for 71.87% (46/64) of the sample, at school for 21.87% (14/64), at group homes for 4.69% (3/64) and one individual was filmed at her day centre. Most (87.50%, 56/64) girls/women were sitting during the video, 7.81% (5/64) were standing, 3.13% (2/64) were taking steps and one alternated between standing still and taking steps. The mother of the female with Rett syndrome was the communication partner in most (67.19%, 43/64)

Table 13. Proportion able to make a choice by sample characteristics.

Characteristic (n)	Able to make a choice n (%)		*p*-value[a]
	Yes	No	
Age group (64)			
≤ 8 years (16)	14 (87.50%)	2 (12.50%)	
8 < 13 years (20)	15 (75.00%)	5 (25.00%)	
13 < 19 years (14)	13 (92.86%)	1 (7.14%)	
≥ 19 years (14)	11 (78.57%)	3 (21.43%)	0.54
Mutation type (64)			
p.Arg106Trp (3)	3 (100.00%)	0	
p.Arg133Cys (6)	5 (83.33%)	1 (16.67%)	
p.Arg168* (6)	5 (83.33%)	1 (16.67%)	
p.Arg255* (6)	4 (66.67%)	2 (33.33%)	
p.Arg270* (9)	7 (77.78%)	2 (22.22%)	
p.Arg294* (6)	5 (83.33%)	1 (16.67%)	
p.Arg306Cys (5)	4 (80.00%)	1 (20.00%)	
p.Thr158Met (4)	4 (100.00%)	0	
C-terminal deletion (6)	5 (83.33%)	1 (16.67%)	
Early truncation (1)	1 (100.00%)	0	
Large deletion (4)	3 (75.00%)	1 (25.00%)	
Other (8)	7 (87.50%)	1 (12.50%)	1.00
Ability to walk (62)			
Independent (32)	26 (81.25%)	6 (18.75%)	
Minimal or Moderate Assistance (13)	11 (84.61%)	2 (15.38%)	
Maximal assistance or unable to walk (17)	14 (82.35%)	3 (17.65%)	1.00
Ability to grasp (58)			
Independent (33)	28 (84.85%)	5 (15.15%)	
Unable to grasp (25)	21 (84.00%)	4 (16.00%)	1.00
Speech-language ability at enrolment into the ARSD[b] (64)			
One or more words (12)	9 (75.00%)	3 (25.00%)	
Babble (33)	29 (87.88%)	4 (12.12%)	
No speech (19)	15 (78.95%)	4 (21.05%)	0.50

[a] *p*-value obtained using Fisher's exact test comparing the proportion of girls/women able to make a choice and different characteristics; [b] Data obtained from parent/caregiver completed questionnaire

videos and the father of the girl/woman was the communication partner in 4.69% (3/64). The remaining videos involved other communication partners who were school, group home or day centre staff members. Most (73.44%, 47/64) videos were filmed by another person that was not the communication partner.

The females with Rett syndrome were most often asked to make a choice between different foods (42.18%, 27/64) or different movies (29.69%, 19/64). Other interactions involved making a choice between different drinks, toys and activities. All communication partners used language with 57.8% (37/64) also using gestures and two using a combination of language, gestures and symbols. All, except one who used photos, asked the female with Rett syndrome to make a choice between concrete objects. The majority of females (93.75%, 60/64) were asked to make a choice between two items; three were asked to make a choice between three items, two individiduals did this successfully and one was asked to make a choice between four items and achieved this successfully.

Of those who communicated their choice, almost all (51/53) looked at the item to indicate their choice (Table 14). Of these, seven first looked at their choice and then back at the communication partner. Just under half (24/53) used one modality to communicate their choice, slightly more than half (28/53) used two modalities and one females used three modalities. Figure 8 illustrates, of the 53 females who made a choice, 25% did so by 5 seconds, 50% by 8 seconds and 75% by 22 seconds. Three quarters of females aged 8 to 13 years demonstrated choice making compared with 93% of females aged 13 to 19 years. The median speed of choice making was fastest for those younger than 8 years ($p=0.08$) (Figure 9).

The girls and women who did not make a choice (17.19%, 11/64) fell into two groups; 1) those who did not appear to acknowledge the items presented, as demonstrated by not looking at the items at any point during the interaction (54.55%, 6/11), and 2) those who looked at the items but made no clear indication as to which one was their choice (45.45%, 5/11). An example of a female from the first group was a girl who was asked to make a choice between a glass of cola and water, the girl did not look at either item but maintained her eye gaze away from the items. An example of someone in the second group was a girl who moved between looking at each item and around the room, without spending more time looking at one item more than the other or using another modality to indicate a choice.

Figure 8. Kaplan-Meier survival curve for the ability to make a choice by time (n=53).

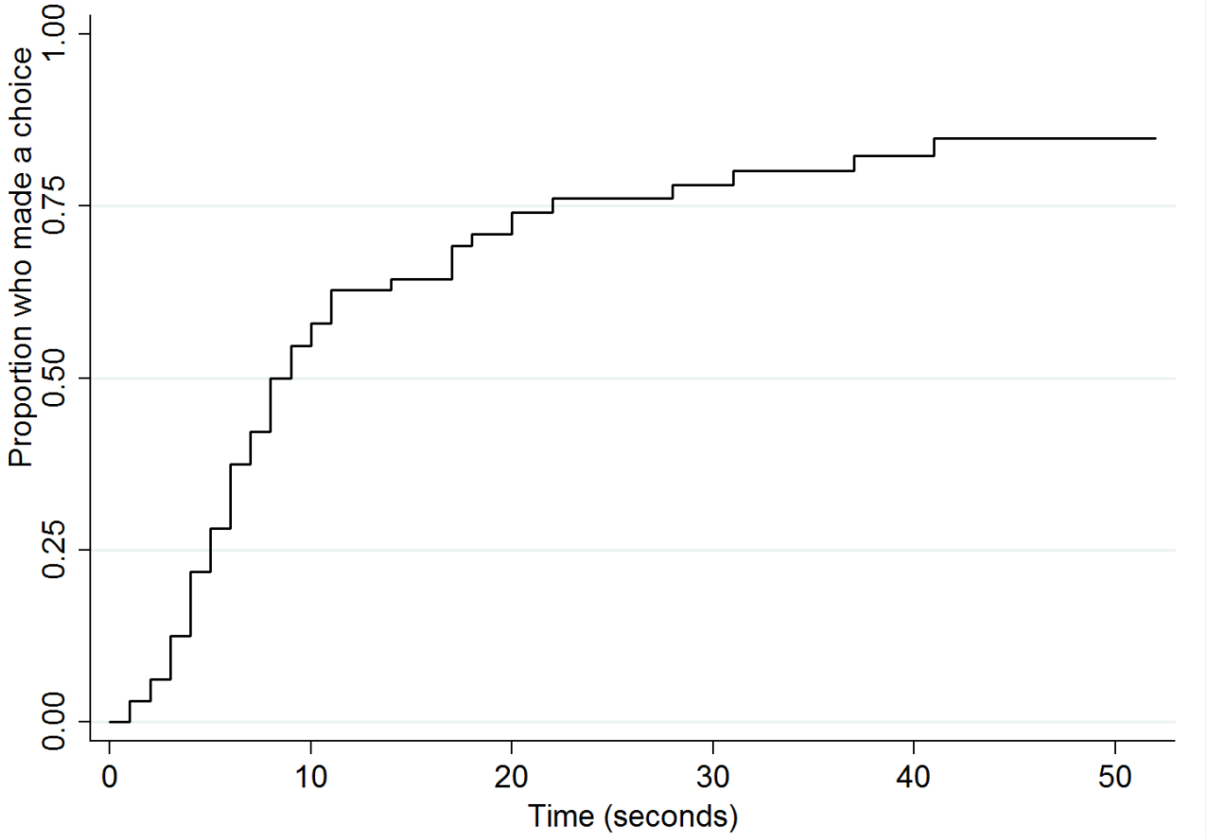


Figure 9. Kaplan-Meier survival curve for the ability to make a choice at different ages, by time (n=53).

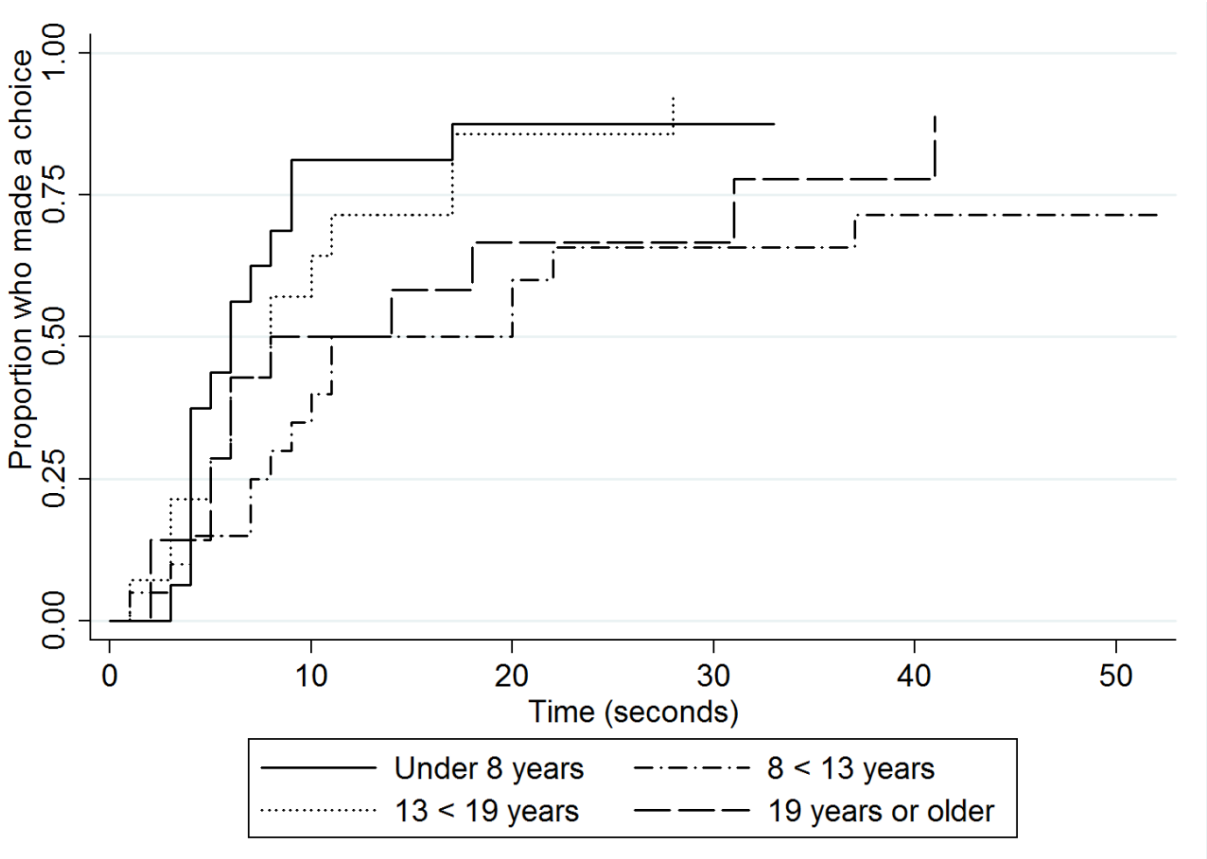


Table 14. The frequency of different communication modalities girls and women with Rett syndrome used to make a choice.

Modality	Frequency[a]
Eye gaze	51
Body movements	
Takes item	7
Leans towards item	4
Gestures	
Gives item to communication partner	1
Points at item	2
Touches item without taking	7
Early sounds	2
Language	2

[a] The frequency will not equal the number of the girls/women who made a choice (n=53) as some girls and women used multiple modalities to indicate their choice

7.5 Discussion

This study described the choice making abilities of girls and women with Rett syndrome by observing video data collected in everyday settings. The majority of our sample seemed to be able to make a choice, in contrast to previous studies that reported between half and two thirds of girls and women with Rett syndrome were able to make choices (Cass et al., 2003; Cianfaglione et al., 2015). We analysed video data of girls and women in familiar environments with familiar communication partners, factors which may positively influence communicative interactions with girls and women with Rett syndrome (Bartolotta et al., 2011; Hetzroni & Rubin, 2006; Ryan et al., 2004). This might explain the higher proportion of girls and women able to make a choice in our study in comparison to previous research using multidisciplinary clinical assessment (Cass et al., 2003) or caregiver questionnaire (Cianfaglione et al., 2015). While the majority in our study made a choice, the time needed to make a choice varied greatly. Time taken to make a choice has not been previously documented in Rett syndrome, although varied response times to a stimulus in general have been reported (Bartolotta et al., 2011). Nevertheless, those who did not make a choice in our study may have not been given enough time to make a choice (Bartolotta et al., 2011) or sufficiently motivated by the items presented (Elefant & Wigram, 2005; Sigafoos et al., 1995).

Approximately half of our sample used a combination of modalities to communicate their choice, of which eye gaze was most frequently used. This provides further evidence for eye gaze as a

communicative strength of girls and women with Rett syndrome (Bartolotta et al., 2011; Didden et al., 2010; Hagberg, 1995). It also validates parent report data on 16 girls and women with Rett syndrome where of the multiple modalities used to communicate, eye gaze was most commonly used for choice making (Urbanowicz et al., 2016). Among those who used eye gaze in our study, seven demonstrated some joint attention by looking at the item and then back at the communication partner (Pence Turnbull & Justice, 2012). This indicates that some females with Rett syndrome may have more advanced eye gaze abilities than others as previously identified in a larger study of females from the ARSD using parent report CSBS DP ITC (Wetherby & Prizant, 2002) data (Urbanowicz, Downs, Girdler, Ciccone, & Leonard, in press). Families and professionals supporting girls and women with Rett syndrome need to be aware of the multiple modalities that may be used to make a choice but that eye gaze appears to be a preference and may therefore be a good target for intervention. Future research protocols need to take the multiple modalities into consideration and not limit choice making definitions to a specific modality.

In our study, the capacity to make a choice did not vary according to age, *MECP2* mutation type, walking ability or hand function, and the time taken to make a choice did not vary according to age group. However the lack of apparent relationships between these factors and the capacity to make a choice and the time taken to make a choice may be due to poor statistical power as a result of our small sample size. Other factors not included in our study, such as the type of reinforcement provided by communication partners (Elefant & Wigram, 2005) and the presence and severity of dyspraxia (Bartolotta et al., 2011), may influence whether or not a girl or woman with Rett syndrome is able to make choices and how quickly the choice is made. Relationships between the communication modalities used by the female with Rett syndrome to make a choice and factors such as *MECP2* mutation type and walking or grasping abilities were not analysed in this study. Nevertheless it is likely that genotype impacts on the type of modalities used as those with the p.Arg133Cys mutation are likely to have a greater use of words (Urbanowicz et al., 2014). Moreover girls and women with greater functional abilities, such as hand use and mobility may have access to a greater repertoire of communication modalities (Urbanowicz et al., 2016). Future research using valid and reliable methods to look at the consistency of choice making over time in different contexts and with different communication partners is needed.

Previous research in Rett syndrome has not detailed the specific communication modalities used by communication partners in their interactions with girls and women with Rett syndrome. We found all communication partners used language in their interactions, over half combined language with

gestures and two combined language with gestures and symbols. This is not surprising given parents/caregivers were instructed to ask the females to indicate her choice. Only two communication partners used symbols in their interactions even though the use of communication aids, including pictures of items, commonly makes choice making occur more often and clearly as reported by SLPs working with girls and women with Rett syndrome (Wandin et al., 2015). It would be interesting to investigate how the communication modalities used by communication partners impact the success of choice making and other important communicative functions to inform future communication interventions.

This is the largest descriptive study to date using video data to demonstrate the choice making abilities of girls and women with Rett syndrome. As a result we have been able to contribute unique information to the existing literature. Nevertheless a number of limitations need to be taken into consideration when interpreting our results. Our study described the ability of the girl or women to make a choice at one point in time and therefore may not represent her usual abilities. Although using a naturalistic context with familiar communication partners to elicit choice making abilities has its strengths, it also means the sampling context was not standardised across participants and this limits comparisons between participants. This also means the way in which the choice was presented varied across interactions which may have impacted in the individual's ability to make a choice and we were unable to test the validity of the participants' choice making (Sigafoos & Dempsey, 1992). Additionally, caregivers were not instructed to wait for a minimum amount of time following their instruction therefore girls and women who did not make a choice may have been able to do so if given more time. Although our coding framework was developed based on a review of the literature and piloted, the researcher may have not coded a choice that parents/caregivers or other familiar communication partners usually respond to (Julien et al., 2014). Finally, although our study is the largest of its kind we still had limited statistical power when analysing relationships between choice making and factors such as *MECP2* mutation type and it is not known if the girls and women excluded from this study were able to make a choice.

We found the majority of girls and women with Rett syndrome can make choices in naturalistic contexts with familiar communication partners. Half of our sample made a choice within eight seconds although one female required four minutes and six seconds to make her choice. Eye gaze was frequently used to communicate choices, sometimes in combination with other communications modalities such as body movements and gestures, and communication partners always used language, sometimes in combination with gestures or symbols. Although we did not find

a relationship between age, *MECP2* mutation type and level of functional abilities and the ability to make a choice, it is still likely these factors may influence the types of modalities used to communicate a choice. Our findings provide further evidence to support the use of communication strategies some families and professionals are already using including waiting for a response and observing for the use of multiple modalities (Urbanowicz et al., 2016; Wandin et al., 2015) but clarify the length of time that may be required.

Chapter 8: Final discussion

8.1 Overview

The overall purpose of this thesis was to describe the performance of communication tasks by girls and women with Rett syndrome and to investigate factors that are positively and negatively associated with communication performance. The ICF-CY (World Health Organization, 2007) was used to guide the literature review and the four studies contained within this thesis. Functioning in one domain of the ICF-CY (i.e. communication) is the result of the complex and bidirectional relationships between the health condition and contextual factors (World Health Organization, 2007). Each study explored a different aspect of communication and relationships between the aspect of communication and components of the ICF-CY (World Health Organization, 2007). Chapter four provided a qualitative exploration of how girls and women communicate in everyday life, describing relationships between impairments of body function and structure, activity limitations and contextual factors from the perspectives of 17 parents. Chapter five interrogated the population-based Australian Rett Syndrome Database (ARSD) and an international database, InterRett, to describe speech-language abilities and explore relationships with genotype. Chapter six also used Australian data to describe the use of eye gaze and gestures, the ability of the girls and women to make requests and investigated relationships with genotype, age and motor abilities. The final results chapter, Chapter seven, used video data to describe the choice making abilities of 64 girls and women and explored relationships with age, genotype, ability to walk and grasp objects and speech-language ability at enrolment into the ARSD.

This research described a number of aspects of communication including different functions of communication (i.e. making a request and a choice) and modalities used to communicate (i.e. eye gaze and gestures) in more detail and with larger sample sizes than previously documented. The studies contained in this thesis have some of the largest sample sizes to date in relation to studies of communication in Rett syndrome, and used clearly defined case inclusion criteria of being female, having a diagnosis of Rett syndrome and a pathogenic *MECP2* mutation which greatly improve the generalisability of findings. Therefore the findings of this thesis contribute greatly to the knowledge of the use of specific communication modalities and functions of communication in girls and women Rett syndrome. The new knowledge generated from this research will allow families, caregivers and professionals to make evidence-based decisions to better support girls and women with Rett syndrome in their communicative interactions in everyday life. This research points to a number of conclusions

and recommendations for future research, professionals working with girls and women with Rett syndrome and the families of girls and women.

8.2 Conclusions

8.2.1 Communication abilities vary in girls and women with Rett syndrome

It is well documented that the severity of Rett syndrome varies greatly amongst affected females. Some girls and women are able to learn and apply knowledge, and perform mobility and self-care activities with mild difficulty whereas others experience severe or complete difficulty (Bebbington et al., 2008; Cass et al., 2003; Cianfaglione et al., 2015). Each study in this thesis investigated the performance of different communication tasks in girls and women with variable clinical severity. Overall, the findings demonstrated variation in communication performance between females with Rett syndrome and also some fluctuations in performance within the same individual.

As demonstrated by the findings of Chapters five and six, the majority of girls and women do not use words (Urbanowicz et al., 2014) or gestures to communicate (Urbanowicz et al., in press). In contrast, almost all girls and women use eye gaze for communication as evidenced by the qualitative findings of Chapter four (Urbanowicz et al., 2016) and quantitative findings of Chapters six (Urbanowicz et al., in press) and seven. These findings largely confirm previous research suggesting eye gaze is a communicative strength of girls and women with Rett syndrome (Bartolotta et al., 2011; Didden et al., 2010; Hagberg, 1995) relative to speech (Bartolotta et al., 2011; Cass et al., 2003) and gestures (Bartolotta et al., 2011; Neul et al., 2014). However the use of eye gaze by females with Rett syndrome still requires interpretation from the communication partner as described in Chapter four were eye gaze was stated by parents as easy to interpret if it was "intense" and "persistent". Furthermore a small proportion of females may have more advanced eye gaze skills than others as evidenced in Chapter seven where seven of the 51 females who used eye gaze to indicate their choice, first looked at their choice and then back at the communication partner. In addition to using eye gaze, females with Rett syndrome were frequently described as using other methods such as leaning and vocalizing in Chapters four and seven. Interestingly few parents mentioned the use of aided AAC in interviews (Urbanowicz et al., 2016) and no AAC devices were used in the video study of choice making abilities despite speech-language pathologists often prescribing aided AAC for girls and women with Rett syndrome (Wandin et al., 2015).

In terms of the function of communication, parents in Chapter four described their daughters as able to engage in meaningful interactions with a range of people in their everyday lives (Urbanowicz et al., 2016). This was supported by findings of the quantitative studies included in Chapters six and seven that found most girls and women often or sometimes requested the attention of others (90%, 136/151) and let others know they needed help or wanted an object out of reach (77%, 115/150) (Urbanowicz et al., in press), and were able to make a choice (83%, 53/64). Prior to the research contained in this thesis, there was a paucity of research investigating these communicative functions in large samples of girls and women with Rett syndrome. For example, two of the largest studies in this area included 87 (Cass et al., 2003) and 91 (Cianfaglione et al., 2015) participants and found 51% (Cass et al., 2003) and 67% (Cianfaglione et al., 2015) were able to make a choice.

The variance observed in communication abilities within this research was related to impairments of body function and structure, activity limitations and contextual factors. The following sections focus on the main conclusions for the observed variation in communication abilities drawn from the studies included within this thesis. The conclusions highlight the important role both genetic and environmental factors play in the development and maintenance of communication abilities and discuss the complex bidirectional relationships between these factors.

8.2.2 Genotype is partly responsible for the variance observed in the use of specific communication modalities

According to the ICF-CY (World Health Organization, 2007) genotype is classified as an impairment of body function and structure. Mutations in the *MECP2* gene were found to cause Rett syndrome in 1999 by Amir and colleagues. Since then numerous studies have provided evidence for relationships between *MECP2* mutation type and the severity of phenotype, but without detailed descriptions of many aspects of communication (Bebbington et al., 2008; Cuddapah et al., 2014; Neul et al., 2008). Findings from Chapters five and six demonstrated that *MECP2* mutation type was related to aspects of speech-language abilities (Urbanowicz et al., 2014) and the communicative use of gestures (Urbanowicz et al., in press). As evidenced in Chapter five, girls with a p.Arg133Cys mutation were the most likely to be able to speak before and after speech-language regression (Urbanowicz et al., 2014). This confirms previous reports of girls and women with a p.Arg133Cys mutation often having the ability to say words (Bebbington et al., 2008; Cuddapah et al., 2014; Leonard et al., 2003). Furthermore Chapter five provided new evidence on the use of babble and found girls with a p.Arg106Trp, p.Arg133Cys, p.Arg168*, p.Arg294* or p.Thr158Met mutation were more likely than those

with a large deletion to babble following a regression in speech-language abilities (Urbanowicz et al., 2014). The study contained in Chapter six found that those with a C-terminal deletion had the best communicative use of gestures in comparison to girls and women with a p.Arg168* mutation (Urbanowicz et al., in press). This adds new information to our existing knowledge of girls with a C-terminal deletion who are generally described as experiencing a mild phenotype with earlier age of walking, later age of onset of stereotypies, normal head circumference and weight, in comparison to girls and women with other *MECP2* mutation types (Bebbington et al., 2010).

This research was the first to examine relationships between the use of eye gaze and *MECP2* mutation type. Encouragingly, it was found that the use of eye gaze was a strength across the majority of girls and women with different *MECP2* mutation types. Eye gaze was used by girls and women with different *MECP2* mutations (Urbanowicz et al., in press) and by almost all girls and women, representing varied *MECP2* mutation types, when making a choice as demonstrated by the findings of the qualitative study (Urbanowicz et al., 2016) and the final study using video data.

Due to the important role MeCP2 plays in the development and maturation of the brain and nervous system (Cohen et al., 2011) it is likely there is a direct relationship between *MECP2* mutation type and the underlying cognitive and language skills required for communication. Yet also, *MECP2* mutation type is known to influence the level of impairment in other functional abilities, including those required to produce speech and gestures, such as mobility (Bebbington et al., 2008; Colvin et al., 2004; Cuddapah et al., 2014). Therefore there is also likely to be a secondary relationship between *MECP2* mutation type and communication, which is mediated by level of impairment in other functional abilities. For example girls and women with a *MECP2* mutation generally associated with an overall less severe phenotype, such as a p.Arg133Cys (Bebbington et al., 2008; Cuddapah et al., 2014) or a C-terminal deletion (Bebbington et al., 2010), were found to also experience less severe impairments of communication. This may because they have the mobility skills to interact with their environment effectively which has a positive effect on the cognitive and language development (Campos et al., 2000; Longobardi, Spataro, & Rossi-Arnaud, 2014). Also they may experience less severe comorbidities such as seizures which may potentially influence communication abilities (Didden et al., 2010; Vignoli et al., 2010). As a result, girls and women with *MECP2* mutation types associated with a mild phenotype may have access to a greater range of communication modalities.

8.2.3 Mobility is related to the use of some communication modalities

The ICF-CY categorises mobility as an activity that includes carrying, moving and handling objects, walking and moving (World Health Organization, 2007). The majority of girls and women with Rett syndrome experience severe limitations in mobility activities including standing, walking (Downs, Bebbington, Jacoby, et al., 2008; Foley et al., 2011) and handling objects (Downs, Bebbington, Jacoby, et al., 2010). Level of mobility impairment has been related to *MECP2* mutation type in Rett syndrome (Bebbington et al., 2008; Downs, Stahult, et al., 2016). Chapter six demonstrated that level of gross motor impairment was related to the use of gestures, after adjusting for *MECP2* mutation type, with those with less impairment more likely to use gestures, in 151 females (Urbanowicz et al., in press). On the other hand, this study demonstrated no significant relationships between level of gross motor impairment and the use of eye gaze as measured by CSBS DP ITC items (Wetherby & Prizant, 2002). These findings are similar to results from a previous study with a smaller sample size of 87 girls and women with Rett syndrome that found better hand function and mobility abilities were correlated with a better overall communication score (Cass et al., 2003). However Cass' study did not report on relationships between mobility activities and individual communication outcomes such as the use of gestures or eye gaze. Qualitative data from parental interviews provided context for the findings of this research with parents stating that being able to walk and functionally use their hands would give their daughter access to additional communication modalities such as walking towards or reaching for preferred items (Urbanowicz et al., 2016).

Motor abilities are required for the production of the communication modalities described above including gestures and other communicative behaviours such as walking towards or reaching for preferred items. Also physical interaction with the environment and other people, which is facilitated by motor abilities, is important in the typical development of cognitive abilities including those required to use gestures (Campos et al., 2000; Longobardi et al., 2014). The majority of girls and women with Rett syndrome are described to experience a level of dyspraxia that may impact on their mobility (Downs et al., 2014) and therefore use of communication modalities (Bartolotta et al., 2011; Woodyatt & Ozanne, 1994). Yet despite the high levels of motor impairments associated with Rett syndrome, many girls and women are still able to use eye gaze as a communicative modality. This is similar to reports of children with severe physical and speech impairments also able to use eye gaze to interact (Borgestig, Sandqvist, Parsons, Falkmer, & Hemmingsson, 2016) and indicate preferences (Fleming et al., 2010). Therefore girls and women should be supported to use eye gaze as a communicative strategy, despite their level of gross motor impairment.

8.2.4 Communication partners play an important role in the success of communicative interactions

An important environmental factor that was found to influence the success of communication in the research was the characteristics of the communication partner, as evidenced by the qualitative study in Chapter four. This study found, according to parents, the knowledge, skills and attitudes of the communication partner are integral to the success of communication interactions (Urbanowicz et al., 2016). Observing the girl or woman for communicative behaviours, waiting for a communicative response, establishing eye contact and providing physical support where required, were identified as key skills to support communication. These findings support and expand on previous research suggesting that the knowledge, skills and attitudes of the communication partner and their interactional style are an important communication success factor, despite genotype and mobility also playing a role (Bartolotta & Remshifski, 2013; Bartolotta et al., 2011; Koppenhaver, Erickson, & Skotko, 2001; Sigafoos, Woodyatt, Tucker, et al., 2000). The final study included in this thesis also found the majority of communication partners used language in combination with other communication modalities such as gestures or symbols which was found to be effective in supporting communication in three girls with Rett syndrome in another study (Ryan et al., 2004).

Parents, in Chapter four, also reported that the attitudes of the communication partner in relation to the cognitive capacity of the girls and women and towards people with disability in general, influenced the success of communication (Urbanowicz et al., 2016). This finding was supported by Bartolotta's (2011) survey which found respondents had different perceptions of the girls' and womens' cognitive and communication capacities. Similarly an observational study, in which familiar and unfamiliar people viewed videos of girls and women with Rett syndrome performing a communication activity, showed that different individuals perceived communication differently (Julien et al., 2014). This suggests although there may be general skills that communication partners can use to improve the success of communicative interactions, their perceptions differ and it is important to document these perceptions so they can be considered within the context of communicative interventions that focus on the communication partner.

8.2.5 Both qualitative and quantitative methods are important in the studyof communication abilities in individuals with severe disability

The study of communication abilities in people with severe disability is complex and this thesis has demonstrated that both qualitative and quantitative methods are useful in developing a

broad and deep understanding in this area of research. The research contained in this thesis used quantitative and qualitative methods to analyse data from a range of sources including interviews with parents, caregiver completed questionnaires and video data, allowing for multiple perspectives to be explored. Chapters five, six and seven utilised quantitative methods and provide some of the best available evidence on aspects of communication such as speech-language abilities and relationships with factors such as *MECP2* mutation type, due to their data collection methods and large sample sizes. Chapter four utilised qualitative methods to explore how girls and women communicate in everyday life and the various facilitators and barriers to communication. This study was the first in-depth qualitative investigation of communication abilities in Rett syndrome and it provides depth, meaning and context to the findings of the quantitative studies. For example the qualitative study provided the additional context for the use of communication in everyday life and the development of relationships with others, as girls and women were described to communicate with a range of people including family members, professionals and friends. The qualitative findings of this research complement and bring greater meaning to the quantitative results alone. Furthermore the use of both types of methodologies allowed for the triangulation of data across studies. Key findings from the research utilising parent interview data such as eye gaze being a communicative strength of the girls and the majority being able to make a choice, were confirmed in the studies contained in Chapters six using questionnaire data and seven utilising video data.

8.2.6 The ICF-CY has some limitations in the study of communication in individuals with severe disability

The ICF-CY (World Health Organization, 2007) provided a framework to explore the multifaceted and complex relationships between communication and impairments in body functions and structure, activity limitations and contextual factors in girls and women with Rett syndrome. The framework was used to guide the collection of data for the literature review and qualitative study, and throughout the research to guide the interpretation of data. It ensured the holistic study of communication and allowed for the evaluation of the complex relationships between communication abilities and components of the ICF-CY (World Health Organization, 2007), and also the exploration of the bidirectional relationships between the factors that influence communication. For example genotype, an impairment in body function and structure, was found to relate directly to the use of speech and gestures. In our interpretation of this data we were also able to consider the known relationship between genotype and motor abilities, of which motor abilities were also found to influence the use of gestures.

Using the the ICF-CY (World Health Organization, 2007) in this research to explore communication in girls and women with Rett syndrome represents a first of its kind. The use of the ICF-CY (World Health Organization, 2007) in this research allowed us to build on the current knowledge of the applicability of the framework in communication disability (O'Halloran & Larkins 2008). A limitation of using the ICF-CY (World Health Organization, 2007) in this research was the framework's inability to define the broad range of communication modalities and functions a person with severe disability may use and communicate. Therefore the Communication Matrix (Rowland, 2004), an instrument designed to evaluate the expressive communication skills of children with severe and multiple disabilities, was used to describe the activity of communication in greater detail than is present in the ICF-CY Communication chapter (World Health Organization, 2007). The use of the ICF-CY (World Health Organization, 2007) together with the Communication Matrix (Rowland, 2004) within this research provided a standard framework and language to allow findings and conclusions across studies to be easily compared and understood. Future research may similarly benefit from the use of a standard framework and language to ensure the Rett syndrome communication literature is more comparable and easier to understand throughout the international community.

8.3 Limitations

The limitations of each study were described in detail in Chapters four to seven. As such this section will provide a brief overview of the limitations of the research. All studies utilised cross sectional data and the findings cannot be used to predict whether communication abilities will be maintained or change over time. Future research would benefit from conducting longitudinal studies to explore communication abilities over time. Chapters four, five and six utilised caregiver reported data which has some inherent biases including caregivers potentially recalling past events inaccurately (Ozonoff et al., 2011; Zwaigenbaum et al., 2013). The potential of such bias was minimised by asking caregivers to report on current functioning and in instances where caregivers were asked to report on earlier functioning, the age of the girls/women were limited to 15 years or younger at the time of study. Although the studies contained in this thesis have the largest samples of their kind in the Rett syndrome literature, the final two studies in Chapter six and seven may have had limited statistical power to detect relationships between *MECP2* mutation type and aspects of communication.

8.4 Recommendations

8.4.1 Recommendations for future research

To extend the findings of this thesis there are several recommendations for future research. Firstly, the generalisability of findings in the current Rett syndrome communication literature (not including the studies published as a result of this thesis) has often been limited by small sample sizes (Bartolotta et al., 2011; Cass et al., 2003; Didden et al., 2010; Halbach et al., 2008; Halbach et al., 2013), poorly described case inclusion criteria (Byiers et al., 2014; Elefant & Lotan, 2004; Stasolla et al., 2014; Stasolla et al., 2015) and the inclusion of cases that do not have a clear diagnosis of Rett syndrome (e.g. the inclusion of a three cases with *MECP2*-related disorder) (Cianfaglione et al., 2015). One recommendation is that researchers collaborate and make use of existing large repositories of data on Rett syndrome including the two databases used in this research, ARSD (Leonard, 1996) and InterRett (Fyfe et al., 2003), and others such as the British Isle Rett Syndrome Survey (BIRSS) (Cianfaglione et al., 2015) the Natural History Study (NSH) within the United States (Neul et al., 2014). Another recommendation would be for these databases to collect core data pertaining to communication abilities to allow comparisons across databases and for researchers to consistently and clearly report how diagnosis of Rett syndrome was confirmed in their sample and the *MECP2* mutation status of participants, as the research contained in this thesis clearly demonstrate relationships between *MECP2* mutation type and aspects of communication. The use of databases with a large sample size, clearly defined parameters for the inclusion of cases in studies and that collect relevant communication data would allow for the further study of the complex relationships between aspects of communication and impairments, activity limitations and contextual factors in well-powered studies and would significantly increase the generalisability and applicability of research findings.

Secondly, it was beyond the scope of this thesis to empirically analyse the receptive communication and cognitive abilities of females with Rett syndrome. However this is an important area for future study as both are likely to impact expressive communication abilities. Both receptive and cognitive abilities are difficult to accurately measure in Rett syndrome as many conventional measures are not appropriate as they do not take into consideration the varied functional abilities of the girls and women (Byiers & Symons, 2012). As demonstrated in this thesis, eye gaze is a communicative strength of girls and women and there is emerging evidence to suggest that eye gaze technology may be a possible avenue for the assessment of receptive communication and cognitive abilities in Rett syndrome (Baptista et al., 2006; Djukic et al., 2012; Rose et al., 2013; Schwartzman, 2013; Townend, Marschik, et

al., 2015). Future research should continue to explore this opportunity to profile the receptive communication and cognitive abilities of girls and women with Rett syndrome and investigate relationships between expressive communication, receptive communication and cognitive abilities.

Thirdly, future research should build on our findings regarding the role communication partners play in the success of communicative interactions. Parents participating in the qualitative study in Chapter four identified a variety of characterstics of communication partners that are important in ensuring the success of a communicative interaction between girls and women with Rett syndrome and others. It would be interesting to further explore the role of each identified characteristic in experimental studies to provide higher level evidence for the communication partner characteristics that are required for successful communication.

Fourthly, it was also beyond the scope of this research to explore the relationships between communication, and participation and quality of life outcomes. Communication abilities have been identified as an important domain for the quality of life for girls and women with Rett syndrome (Epstein et al., 2016) and research involving children with cerebral palsy suggests motor and speech-language impairments reduce levels of participation in everyday life (Schenker, Coster, & Parush, 2005). Enabling people with disability to participate in all aspects of life and experience a good quality of life is an important human rights issue (United Nations, 2006; United Nations Economic and Social Commission for Asia and the Pacific, 2012). Therefore research is warranted to further explore the impact communication abilities has on participation in everyday life and quality of life in girls and women with Rett syndrome with the ultimate goal of improvement in participation and quality of life.

Finally, researchers should not disregard the importance of caregiver data in the complex study of communication in individuals with severe disability. Often caregivers are the individual's primary communication partner and therefore their perspectives are integral to providing a depth of understanding of communication abilities that would not be observed from quantitative clinical data alone. As such, researchers should consider the adoption of both qualitative and quantitative methodsto allow for a broad and in depth analysis of communication abilities in severe disability.

8.4.2 Recommendations for clinical practice

The findings of this thesis provide some of the highest quality data on a number of aspects of communication and as such have numerous implications for professionals working with girls and women with Rett syndrome. Health professionals, particularly speech-language pathologists, play an important role in informing and supporting caregivers and other communication partners in maximising the communicative potential of girls and women with Rett syndrome. However due to the relative rarity of Rett syndrome the clinical experience of health professionals is often limited, particularly for those working outside of specialised Rett syndrome clinics. As such, reliable and valid sources of information on the communicative abilities of girls and women with Rett syndrome are required to inform clinical practice.

The following recommendations for professionals should be viewed in light of evidence for best practice when working with individuals with severe disability in the area of communication. This includes, but is not limited to, ensuring the individual with Rett syndrome and their caregivers are key members of the team and that they drive the decision making. Decisions regarding the management of communication should be consumer driven and focused on the individual needs of each girl or woman with Rett syndrome and their family and not just focus on the knowledge the professional may impart on the family (American Speech-Language-Hearing Association, 2002).

Professionals need to consider the communicative strengths and limitations of girls and women with Rett syndrome, and the numerous impairments of body function and structure (e.g. genotype), activity limitations (e.g. mobility) and contextual factors (e.g. the knowledge and skills of the communication partner) that may impact the performance of communication activities at any given point in time. Due to the complex nature of Rett syndrome, many girls and women access the support of a variety of allied health professionals including speech-language pathologists, occupational therapists and physiotherapists (Bartolotta et al., 2011). Therefore joint multi-disciplinary assessments covering aspects of communication may be feasible and would allow for a comprehensive assessment of communication abilities whilst taking into consideration the other functional abilities of the girl or woman that play a role in communication such as mobility and hand function. Additionally, considering information from a variety of sources including caregivers and observations would be beneficial. Where possible, we also recommend multiple assessments due to fluctuations often observed in the performance of communication activities within the same individual with Rett syndrome. Interestingly, we found few girls and women used aided AAC to make a choice in the final

study using video data or were described by parents as using aided AAC in the qualitative study, despite aided AAC being considered useful and helpful by speech-language pathologists (Wandin et al., 2015). This may mean that outside structured clinical sessions with a professional, few girls and women used aided AAC in everyday contexts with their caregivers. Professionals need to be aware of this when working with families and plan for generalisablity of aided AAC use into other everyday contexts within the home.

8.4.3 Recommendations for caregivers

Caregivers are often the primary communication partner of girls and women with Rett syndrome and therefore play an important role in shaping communicative interactions and in informing others about how their daughters communicate. This research illustrated the valuable contribution of caregiver data, in addition to other data collection methods such as observations, in understanding communication performance. Parent report data was supported by findings of the final study in this thesis that applied a coding framework developed by researchers to quantitatively code video data. Knowing that what they are reporting has validity, can help empower caregivers to advocate for the communication rights of girls and women with Rett syndrome in their lives. Furthermore future research would benefit from continued involvement of caregivers to ensure research is meaningful and applicable to their daily lives.

8.5 Knowledge translation

A widely accepted definition of knowledge translation comes from the Canadian Institutes of Health Research (2015) who define it as “a dynamic and iterative process that includes the synthesis, dissemination, exchanges, and ethically-sound application of knowledge to improve the health of Canadians, provide more effective health services and products, and strengthen the healthcare system”. However, often knowledge generated from research is not translated into practice and therefore does not always equate to improved outcomes for the individual and their community. Throughout the research included in this thesis effort was made to translate the findings of this research into practice by disseminating research findings to a variety of audiences including researchers, health and education professionals, and families to influence their practice and interactions with girls and women with Rett syndrome. Research findings have been presented at a number of national and international conferences with different target audiences including researchers, professionals and caregivers (see pages viii - ix for details). Easy to read summaries of published articles have also been developed and

made available for the broader community, including families and caregivers, on the Australian Rett Syndrome Database website: www.aussierett.org.au. Furthermore the findings of this research informed the development of lectures on the topic of Rett syndrome, delivered by the candidate, to 4th year occupational therapy students. This ensures students are equipped with up-to-date knowledge prior to commencing clinical practice.

The findings of this research will also inform the development of clinical guidelines for the management of communication in individuals with Rett syndrome. Under the direction of Professor Leopold Curfs, the candidate, with a team of colleagues from around the globe was successful in obtaining a HeART (Help Accelerate RTT Therapeutics) grant from rettsyndrome.org to fund this project (rettsyndrome.org, 2016). The clinical guidelines will be developed using a consensus approach which will involve a comprehensive literature review and wide consultation with key stakeholders using the Delphi method (Boulkedid, Abdoul, Loustau, Sibony, & Alberti, 2011). The guidelines will provide much needed information and direction for professionals and caregivers in the management of communication and will ensure consistent information is provided to families around the world.

8.6 Final comments

Communication skills have been identified as an important aspect of quality of life for girls and women with Rett syndrome (Epstein et al., 2016). The work contained in this thesis adds significantly to the existing body of knowledge on the communication abilities of girls and women with Rett syndrome. Prior to this research, there was a paucity of literature describing aspects of communication and the numerous and varied facilitators and barriers to communicative success. We can now say with greater certainty than ever before that girls and women with Rett syndrome share communicative strengths including the use of eye gaze and the ability to choose, and in contrast, words or gesture are rarely used, reflecting genotype and motor abilities.

References

Ager, S., Fyfe, S., Christodoulou, J., Jacoby, P., Schmitt, L., & Leonard, H. (2006). Predictors of scoliosis in Rett syndrome. *Journal of Child Neurology, 21*(9), 809-813. doi: 10.1177/08830738060210091501

Alamillo, A. R., Colletta, J.-M., & Guidetti, M. (2013). Gesture and language in narratives and explanations: the effects of age and communicative activity on late multimodal discourse development. *Journal of Child Language, 40*(03), 511-538. doi: 10.1017/S0305000912000062

American Speech-Language-Hearing Association. (2002). Augmentative and alternative communication: Knowledge and skills for service delivery. Retrieved 1 August 2016, from http://www.asha.org/policy/KS2002-00067/

Amir, R. E., Van den Veyver, I. B., Wan, M., Tran, C. Q., Francke, U., & Zoghbi, H. Y. (1999). Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nature Genetics, 23*(2), 185-188. doi: 10.1038/13810

Anderson, A., Wong, K., Jacoby, P., Downs, J., & Leonard, H. (2014). Twenty years of surveillance in Rett syndrome: what does this tell us? *Orphanet Journal of Rare Diseases, 9*(1), 1-9. doi: 10.1186/1750-1172-9-87

Archer, H., Evans, J., Leonard, H., Colvin, L., Ravine, D., Christodoulou, J., . . . Clarke, A. (2006). Correlation between clinical severity in patients with Rett syndrome with a p.R168X or p.T158M MECP2 mutation, and the direction and degree of skewing of X-chromosome inactivation. *Journal of Medical Genetics, 44*, 148-152. doi: 10.1136/jmg.2006.045260

Atkinson, H. L., & Nixon-Cave, K. (2011). A tool for clinical reasoning and reflection using the International Classification of Functioning, Disability and Health (ICF) Framework and patient management model. *Physical Therapy, 91*(3), 416-430. doi: 10.2522/ptj.20090226

Bao, X., Downs, J., Wong, K., Williams, S., & Leonard, H. (2013). Using a large international sample to investigate epilepsy in Rett syndrome. *Developmental Medicine & Child Neurology, 55*(6), 553-558. doi: 10.1111/dmcn.12093

Baptista, P. M., Mercadante, M. T., Macedo, E. C., & Schwartzman, J. S. (2006). Cognitive performance in Rett syndrome girls: A pilot study using eyetracking technology. *Journal of Intellectual Disability Research, 50*(9), 662-666. doi: 10.1111/j.1365-2788.2006.00818.x

Bartl-Pokorny, K., Marschik, P., Sigafoos, J., Tager-Flusberg, H., Kaufmann, W., Grossmann, T., & Einspieler, C. (2013). Early socio-communicative forms and functions in typical Rett

syndrome. *Research in Developmental Disabilities, 34*, 3133-3138. doi: 10.1016/j.ridd.2013.06.040

Bartolotta, T. E., & Remshifski, P. A. (2013). Coaching communication partners: A preliminary investigation of communication intervention during mealtime in Rett syndrome. *Communication Disorders Quarterly, 34*(3), 162-171. doi: 10.1177/1525740112453165

Bartolotta, T. E., Zipp, G. P., Simpkins, S. D., & Glazewski, B. (2011). Communication skills in girls with Rett syndrome. *Focus on Autism and Other Developmental Disabilities, 26*(1), 15-24. doi: 10.1177/1088357610380042

Battaglia, M., Russo, E., Bolla, A., Chiusso, A., Bertelli, S., Pellegri, A., Borri, G., & Martinuzzi, A. (2004). International Classification of Functioning, Disability and Health in a cohort of children with cognitive, motor, and complex disabilities. *Developmental Medicine & Child Neurology, 46*, 98-106. doi: 10.1017/S0012162204000209

Bebbington, A., Anderson, A., Ravine, D., Fyfe, S., Pineda, M., de Klerk, N., . . . Leonard, H. (2008). Investigating genotype-phenotype relationships in Rett syndrome using an international data set. *Neurology, 70*, 868-875. doi: 10.1212/01.wnl.0000304752.50773.ec

Bebbington, A., Downs, J., Percy, A., Pineda, M., Ben Zeev, B., Bahi-Buisson, N., & Leonard, H. (2012). The phenotype associated with a large deletion on MECP2. *European Journal of Human Genetics, 20*, 921-927. doi: 10.1038/ejhg.2012.34

Berger-Sweeney, J. (2011). Cognitive deficits in Rett syndrome: What we know and what we need to know to treat them. *Neurobiology of Learning and Memory, 96*(4), 637-646. doi: 10.1016/j.nlm.2011.05.006

Bölte, S., de Schipper, E., Robison, J. E., Wong, V. C. N., Selb, M., Singhal, N., . . . Zwaigenbaum, L. (2014). Classification of Functioning and Impairment: The Development of ICF Core Sets for Autism Spectrum Disorder. *Autism Research, 7*(1), 167-172. doi: 10.1002/aur.1335

Borgestig, M., Sandqvist, J., Parsons, R., Falkmer, T., & Hemmingsson, H. (2016). Eye gaze performance for children with severe physical impairments using gaze-based assistive technology - A longitudinal study. *Assistive Technology, 28*(2), 93-102. doi: 10.1080/10400435.2015.1092182

Boulkedid, R., Abdoul, H., Loustau, M., Sibony, O., & Alberti, C. (2011). Using and reporting Delphi methd for selecting healthcare quality indicators: A systematic review. *PLoS ONE, 6*(6), 1-9. doi: 10.1371/journal.pone.0020476

Brady, N., & Halle, J. (1997). Functional analysis of communcative behaviours. *Focus on Autism and Other Developmental Disabilities, 12*(2), 95-104.

Brady, N., Marquis, J., & Fleming, K. (2004). Prelinguistic predictors of language growth in children with developmental disabilities. *Journal of Speech, Language, and Hearing Research, 47*, 663-677. doi: 10.1044/1092-4388(2004/051)

Brady, N., Skinner, D., Roberts, J., & Hennon, E. (2006). Communication in young children with Fragile X syndrome: A qualitative study of mothers' perspectives. *American Journal of Speech-Language Pathology, 15*(4), 353-364. doi: 10.1044/1058-0360(2006/033)

Budden, S. (2012). Clinical variability in early speech-language development in females with Rett syndrome. *Developmental Medicine & Child Neurology, 54*(5), 392-393. doi: 10.1111/j.1469-8749.2012.04246.x

Bunning, K., Smith, C., Kennedy, P., & Greenham, C. (2013). Examination of the communication interface between students with severe to profound and multiple intellectual disability and educational staff during structured teaching sessions. *Journal of Intellectual Disability Research, 57*(1), 39-52. doi: 10.1111/j.1365-2788.2011.01513.x

Byiers, B., Dimian, A., & Symons, F. J. (2014). Functional communication training in Rett syndrome: A preliminary study. *American Journal on Intellectual and Developmental Disabilities, 119*(4), 340-350. doi: 10.1352/1944-7558-199.4.340

Byiers, B., & Symons, F. J. (2012). Issues in Estimating Developmental Level and Cognitive Function in Rett Syndrome. In R. M. Hodapp (Ed.), *International Review of Research in Developmental Disabilities* (Vol. 43, pp. 147-185). San Diego: Elsevier Academic Press Inc.

Calculator, S. N. (2002). Use of enhanced natural gestures to foster interactions between children with Angelman syndrome and their parents. *American Journal of Speech-Language Pathology, 11*(4), 340-355. doi: 10.1044/1058-0360(2002/039)

Campos, J. J., Anderson, D. I., Barbu-Roth, M. A., Hubbard, E. M., Hertenstein, M. J., & Witherington, D. (2000). Travel Broadens the Mind. *Infancy, 1*(2), 149-219. doi: 10.1207/s15327078in0102_1

Canadian Institutes of Health Research. (2015). Knowledge translation. Retrieved 10 April 2016, from www.cihr-irsc.gc.ca/e/29418.html

Capone, N. C., & McGregor, K. K. (2004). Gesture DevelopmentA Review for Clinical and Research Practices. *Journal of Speech, Language, and Hearing Research, 47*(1), 173-186. doi: 10.1044/1092-4388(2004/015)

Cascella, P. W. (2014). Tangible object symbols: A case study with an adult with multiple disabilities. *Journal of Visual Impairment & Blindness, 108*(3), 249-253.

Cass, H., Reilly, S., Owen, L., Wisbeach, A., Weekes, L., Slonims, V., . . . Charman, T. (2003). Findings from a multidisciplinary clinical case series of females with Rett syndrome.

Developmental Medicine & Child Neurology, 45, 325-337. doi: 10.1017/S0012162203000616

Chae, J. H., Hwang, H., Hwang, Y. S., Cheong, H. J., & Kim, K. J. (2004). Influence of MECP2 gene mutation and X-chromosome inactivation on the Rett syndrome phenotype. *Journal of Child Neurology, 19*(7), 503-508. doi: 10.1177/08830738040190070501

Christodoulou, J., Grimm, A., Maher, T., & Bennetts, B. (2003). RettBASE: The IRSA MECP2 variation database - A new mutation database in evolution. *Human Mutation, 21*(5), 466-472. doi: 10.1002/Humu.10194

Cianfaglione, R., Clarke, A., Kerr, M., Hastings, R. P., Oliver, C., & Felce, D. (2015). A national survey of Rett syndrome: age, clinical characteristics, current abilities, and health. *American Journal of Medical Genetics Part A, 167*(7), 1493-1500. doi: 10.1002/ajmg.a.37027

Cohen, J. (1960). A coefficient of agreement for nominal scales. *Educational and psychological measurement, 20*(37). doi: 10.1177/001316446002000104

Cohen, S., Gabel, H. W., Hemberg, M., Hutchinson, A. N., Sadacca, L. A., Ebert, D. H., . . . Greenberg, M. E. (2011). Genome-wide activity-dependent MeCP2 phosphorylation regulates nervous system development and function. *Neuron, 72*(1), 72-85. doi: 10.1016/j.neuron.2011.08.022

Colvin, L., Leonard, H., De Klerk, N., Davis, M., Weaving, L., Williamson, S., & Christodoulou, J. (2004). Refining the phenotype of common mutations in Rett syndrome. *Journal of Medical Genetics, 41*, 25-30. doi: 10.1136/jmg.2003.011130

Cuddapah, V. A., Pillai, R. B., Shekar, K. V., Lane, J. B., Motil, K. J., Skinner, S. A., . . . Olsen, M. L. (2014). Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome. *Journal of Medical Genetics, 51*(3), 152-158. doi: 10.1136/jmedgenet-2013-102113

Dahlgren Sandberg, A., Ehlers, S., Hagberg, B., & Gillberg, C. (2000). The Rett syndrome complex: Communicative functions in relation to developmental level and autistic features *Autism, 4*(3), 249-267. doi: 10.1177/1362361300004003003

De Bona, C., Zappella, M., Hayek, G., Meloni, I., Vitelli, F., Bruttini, M., . . . Renieri, A. (2000). Preserved speech variant is allelic of classic Rett syndrome. *European Journal of Human Genetics, 8*(5), 325-330.

Deliberato, D., & Manzini, E. J. (2012). Identification of the Communicative Abilities of Brazilian Children with Cerebral Palsy in the Family Context. *Communication Disorders Quarterly, 33*(4), 195-201. doi: 10.1177/1525740110384130

Didden, R., Korzilius, H., Smeets, E., Green, V. A., Lang, R., Lancioni, G. E., & Curfs, L. M. (2010). Communication in individuals with Rett syndrome: An assessment of forms and

functions. *Journal of Developmental and Physical Disabilities, 22*, 105-118. doi: 10.1007/s10882-009-9168-2

Didden, R., Sigafoos, J., Korzilius, H., Baas, A., Lancioni, G. E., O'Reilly, M. F., & Curfs, L. (2009). Form and function of communicative behaviours in individuals with Angelman syndrome. *Journal of Applied Research in Intellectual Disabilities, 22*, 526-537.

Djukic, A., & McDermott, M. (2012). Social preferences in Rett syndrome. *Pediatric Neurology, 46*, 240-242. doi: 10.1016/j.pediatrneurol.2012.01.011

Djukic, A., McDermott, M., Mavrommatis, K., & Martins, C. (2012). Rett syndrome: Basic features of visual processing - A pilot study of eye-tracking. *Pediatric Neurology, 47*, 25-29. doi: 10.1016/j.pediatrneurol.2012.04.009

Downs, J., Bebbington, A., Jacoby, P., Msall, M., McIlroy, O., Fyfe, S., . . . Leonard, H. (2008). Gross motor profile in Rett syndrome as determined by video analysis. *Neuropediatrics, 39*, 205-210. doi: 10.1055/s-0028-1104575

Downs, J., Bebbington, A., Jacoby, P., Williams, A., Ghosh, S., Kaufmann, W., & Leonard, H. (2010). Level of purposeful hand function as a marker of clinical severity in Rett syndrome. *Developmental Medicine & Child Neurology*. doi: 10.1111/j.1469-8749.2010.03636.x

Downs, J., Bebbington, A., Kaufmann, W., & Leonard, H. (2010). Longitudinal hand function in Rett syndrome. *Journal of Child Neurology, 26*(3), 334-340. doi: 10.1177/0883073810381920

Downs, J., Bebbington, A., Woodhead, H., Jacoby, P., Jian, L., Jefferson, A., & Leonard, H. (2008). Early determinants of fractures in Rett syndrome. *Pediatrics, 121*(3), 540-546. doi: 10.1542/peds.2007-1641

Downs, J., Geranton, S. M., Bebbington, A., Jacoby, P., Bahi-Biusson, N., Ravine, D., & Leonard, H. (2010). Linking MECP2 and pain sensitivity: The example of Rett syndrome. *American Journal of Medical Genetics Part A, 152*(5), 1197-1205. doi: 10.1002/ajmg.a.33314

Downs, J., & Leonard, H. (2013). Longitudinal and population-based approaches to study the lifelong trajectories of children with neurodevelopmental conditions. In G. M. Ronen & P. L. Rosenbaum (Eds.), *Clinics in Developmental Medicine: Life Quality Outcomes in Children and Young People with Neurological and Developmental Conditions: Concepts, Evidence and Practice.* London, Great Britain: Mac Keith Press.

Downs, J., Parkinson, S., Ranelli, S., Leonard, H., Diener, P., & Lotan, M. (2014). Perspectives on hand function in girls and women with Rett syndrome. *Developmental Neurorehabilitation, 17*(3), 210-217. doi: 10.3109/17518423.2012.758183

Downs, J., Stahult, M., Wong, K., Syhler, B., Bisgaard, A.-M., Jacoby, P., & Leonard, H. (2016). Validating the Rett syndrome Gross Motor Scale. *PLoS ONE, 11*(1), 1-11. doi: 10.1371/journal.pone.0147555

Downs, J., Torode, I., Wong, K., Ellaway, C., Elliott, E., Christodoulou, J., . . . Leonard, H. (2016). The natural history of scoliosis in females with Rett syndrome. *Spine, 41*(10), 856-863. doi: 10.1097/BRS.0000000000001399

Duker, P. C., van Driel, S., & van de Bercken, J. (2002). Communication profile of individuals with Down's syndrome, Angelman syndrome and pervasive developmental disorder. *Journal of Intellectual Disability Research, 46*(1), 35-40.

Eadie, P. A., Ukoumunne, O., Skeat, J., Prior, M. R., Bavin, E., Bretherton, L., & Reilly, S. (2010). Assessing early communication behaviours: Structure and validity of the Communication and Symbolic Behaviour Scales - Developmental Profile (CSBS-DP) in 12-month-old infants. *International Journal of Language & Communication Disorders, 45*(5), 572-585. doi: 10.3109/13682820903277944

Elefant, C., & Lotan, M. (2004). Rett syndrome: Dual intervention - Music and physical therapy. *Nordic Journal of Music Therapy, 13*(2), 172-182. doi: 10.1080/08098130409478114

Elefant, C., & Wigram, T. (2005). Learning ability in children with Rett syndrome. *Brain & Development, 27*, S97-S101. doi: 10.1016/j.braindev.2005.03.020

Epstein, A., Leonard, H., Davis, E., Williams, K., Reddihough, D., Murphy, N., . . . Downs, J. (2016). Conceptualizing a quality of life framework for girls with Rett syndrome using qualitative methods. *American Journal of Medical Genetics Part A, 170*(3), 645-653. doi: 10.1002/ajmg.a.37500

Fabio, R. A., Castelli, I., Marchetti, A., & Antonietti, A. (2013). Training communication abilities in Rett Syndrome through reading and writing. *Frontiers in Psychology, 4*, 1-9. doi: 10.3389/fpsyg.2013.00911

Fabio, R. A., Giannatiempo, S., Antonietti, A., & Budden, S. (2009). The role of stereotypies in overselectivity process in Rett syndrome. *Research in Developmental Disabilities, 30*(1), 136-145. doi: 10.1016/j.ridd.2008.01.003

Fabio, R. A., Giannatiempo, S., Oliva, P., & Murdaca, A. (2011). The increase of attention in Rett syndrome: A pre-test/post-test research design. *Journal of Developmental and Physical Disabilities, 23*, 99-111. doi: 10.1007/s10882-010-9207-z

Fehr, S., Bebbington, A., Ellaway, C., Rowe, P., Leonard, H., & Downs, J. (2011). Altered attainment of developmental milestones influences the age of diagnosis of Rett syndrome. *Journal of Child Neurology, 26*(8), 980-987. doi: 10.1177/0883073811401396

Fehr, S., Bebbington, A., Nassar, N., Downs, J., Ronen, G., de Klerk, N., & Leonard, H. (2011). Trends in the diagnosis of Rett syndrome in Australia. *Pediatric Research, 70*(3), 313-319. doi: 10.1203/PDR.0b013e3182242461

Fehr, S., Downs, J., Bebbington, A., & Leonard, H. (2010). Atypical presentations and specific genotypes are associated with a delay in diagnosis in females with Rett syndrome. *American Journal of Medical Genetics Part A, 152A*, 2535-2542. doi: 10.1002/ajmg.a.33640

Fehr, S., Wilson, M., Downs, J., Williams, S., Murgia, A., Sartori, S., . . . Christodoulou, J. (2013). The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy. *European Journal of Human Genetics, 21*(3), 266-273. doi: 10.1038/ejhg.2012.156

Feuerstein, R., Rand, Y., & Rynders, J. (1988). *Don't accept me as I am. Helping retarded people to excel.* Baltimore, MD: University Park Press.

Fischer, M. H., & Zwaan, R. A. (2008). Embodied language: A review of the role of the motor system in language comprehension. *The Quarterly Journal of Experimental Psychology, 61*(6), 825-850. doi: 10.1080/17470210701623605

Fleming, C. V., Wheeler, G. M., Cannella-Malone, H. I., Basbagill, A. R., Chung, Y. C., & Day, K. G. (2010). An evaluation of the use of eye gaze to measure preference of individuals with severe physical and developmental disabilities. *Developmental Neurorehabilitation, 13*(4), 266-275. doi: 10.3109/17518421003705706

Foley, K.-R., Downs, J., Bebbington, A., Jacoby, P., Girdler, S., Kaufmann, W., & Leonard, H. (2011). Change in gross motor abilities of girls and women with Rett syndrome over a 3- to 4-year period. *Journal of Child Neurology*. doi: 10.1177/0883073811402688

Foley, K.-R., Dyke, P., Girdler, S., Bourke, J., & Leonard, H. (2012). Young adults with intellectual disability transitioning from school to post-school: A literature review framed within the ICF. *Disability and Rehabilitation, 34*(20), 1747-1764. doi: 10.3109/09638288.2012.660603

Fyfe, S., Cream, A., de Klerk, N., Christodoulou, J., & Leonard, H. (2003). InterRett and RettBASE: International Rett syndrome association databases for Rett syndrome. *Journal of Child Neurology, 18*(10), 709-713. doi: 10.1177/08830738030180100301

Fyfe, S., Downs, J., McIlroy, O., Burford, B., Lister, J., Reilly, S., . . . Leonard, H. (2007). Development of a video-based evaluation tool in Rett syndrome. *Journal of Autism and Developmental Disorders, 37*(9), 1636-1646.

Hagberg, B. (1995). Rett syndrome: Clinical peculiarities and biological mysteries. *Acta Peadiatrica, 84*, 971-976.

Hagberg, B. (2002). Clinical manifestations and stages of Rett syndrome. *Mental Retardation and Developmental Disabilities Research Reviews, 8*(2), 61-65. doi: 10.1002/mrdd.10020

Hagberg, B., Aicardi, J., Dias, K., & Ramos, O. (1983). A progressive syndrome of autism, dementia, ataxia and loss of purposeful hand use in girls: Rett's syndrome: Report of 35 cases. *Annals of Neurology, 14*, 471-479.

Hagberg, B., Goutières, F., Hanefeld, F., Rett, A., & Wilson, J. (1985). Rett syndrome: Criteria for inclusion and exclusion. *Brain & Development, 7*(3), 372-373. doi: 10.1016/S0387-7604(85)80048-6

Hagberg, B., Hanefeld, F., Percy, A., & Skjeldal, O. L. A. (2002). An update on clinically applicable diagnostic criteria in Rett syndrome: Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting Baden Baden, Germany, 11 September 2001. *European Journal of Paediatric Neurology, 6*(5), 293-297. doi: 10.1053/ejpn.2002.0612

Hagberg, B., & Skjedal, O. H. (1994). Rett variants: A suggested model for inclusion criteria. *Pediatric Neurology, 11*(1), 5-11.

Halbach, N. S. J., Smeets, E. E. J., Schrander-Stumpel, C. T. R. M., van Schrojenstein Lantman de Valk, H. H. J., Maaskant, M. A., & Curfs, L. M. G. (2008). Aging in people with specific genetic syndromes: Rett syndrome. *American Journal of Medical Genetics Part A, 146A*(15), 1925-1932. doi: 10.1002/ajmg.a.32361

Halbach, N. S. J., Smeets, E. E. J., Steinbusch, C., Maaskant, M. A., van Waardenburg, D., & Curfs, L. M. G. (2013). Aging in Rett syndrome: a longitudinal study. *Clinical Genetics, 84*(3), 223-229. doi: 10.1111/cge.12063

Hetzroni, O., & Rubin, C. (2006). Identifying patterns of communicative behaviours in girls with Rett syndrome. *Augmentative and Alternative Communication, 22*(1), 48-61. doi: 10.1080/17461390500387320

Hetzroni, O., Rubin, C., & Konkol, O. (2002). The use of assistive technology for symbol identification by children with Rett syndrome. *Journal of Intellectual & Developmental Disability, 27*(1), 57-71. doi: 10.1080/13668250120119626-1

Hickson, L., Allen, J., Beswick, R., Fulton, M., Wolf, D., Worrall, L., & Scarinci, N. (2008). Relationships between hearing disability, quality of life and wellbeing in older community-based Australians. *The Australian and New Zealand Journal of Audiology, 30*(2), 99-112.

Hostyn, I., & Maes, B. (2009). Interaction between persons with profound intellectual and multiple disabilities and their partners: A literature review. *Journal of Intellectual & Developmental Disability, 34*(4), 296-312. doi: 10.3109/13668250903285648

Howe, T. J. (2008). The ICF contextual factors related to speech-language pathology. *International Journal of Speech-Language Pathology, 10*(1-2), 27-37. doi: 10.1080/1441704070177482

Hsieh, H., & Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qualitative Health Research, 15*(9), 1277-1288. doi: 10.1177/1049732305276687

Huppke, P., Held, M., Hanefeld, F., Engel, W., & Laccone, F. (2002). Influence of mutation type and location on phenotype in 123 patients with Rett syndrome. *Neuropediatrics, 33*, 63-68.

Iacono, T., Carter, M., & Hook, J. (1998). Indentification of intentional communication in students with severe and multiple disabilities. *Augmentative and Alternative Communication, 14*, 102-114. doi: 0743-4618/98/1402-0102

Jeffs, L., Dhalla, I., Cardoso, R., & Bell, C. M. (2014). The perspectives of patients, family members and healthcare professionals on readmissions: Preventable or inevitable? *Journal of Interprofessional Care, 28*(6), 507-512. doi: 10.3109/13561820.2014.923988

Julien, H. M., Parker-McGowan, Q., Byiers, B. J., & Reichle, J. (2014). Adult Interpretations of Communicative Behavior in Learners with Rett Syndrome. *Journal of Developmental and Physical Disabilities*, 1-16. doi: 10.1007/s10882-014-9407-z

Kaplan, E. L., & Meier, P. (1985). Nonparametric estimation from incomplete observersations. *Journal of the American Statistical Association, 53*(282), 457-481.

Keen, D., Sigafoos, J., & Woodyatt, G. (2001). Replacing Prelinguistic Behaviors with Functional Communication. *Journal of Autism and Developmental Disorders, 31*(4), 385.

Kerr, A., Archer, H., Evans, J., Prescott, R., & Gibbon, F. (2006). People with MECP2 mutation-positive Rett disorder who converse. *Journal of Intellectual Disability Research, 50*(5), 386-394. doi: 10.1111/j.1356-2788.2005.00786.x

Knott, M., Leonard, H., & Downs, J. (2011). The diagnostic odyssey to Rett syndrome: The experience of an Australian family. *American Journal of Medical Genetics Part A, 9999*, 1-3. doi: 10.1002/ajmg.a.34372

Koppenhaver, D. A., Erickson, K. A., Harris, B., McLellan, J., Skotko, B. G., & Newton, R. A. (2001). Storybook-based communication intervention for girls with Rett syndrome and their mothers. *Disability and Rehabilitation, 23*(3-4), 149-159.

Koppenhaver, D. A., Erickson, K. A., & Skotko, B. G. (2001). Supporting communication of girls with Rett syndrome and their mothers in storybook reading. *International Journal of Disability, Development and Education, 48*(4), 395-410.

Kortüm, F., Das, S., Flindt, M., Morris-Rosendahl, D. J., Stefanova, I., Goldstein, A., . . . Dobyns, W. B. (2011). The core FOXG1 syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus

callosum hypogenesis. *Journal of Medical Genetics, 48*(6), 396-406. doi: 10.1136/jmg.2010.087528

Lai, D.-C., Chiang, C.-H., Hou, Y.-M., Liu, J.-H., Yao, S.-F., Guo, H.-R., & Tseng, Y.-C. (2014). Predictors of effectiveness of early intervention on children with intellectual disability: a retrospective cohort study. *BMC Pediatrics, 14*, 170-170. doi: 10.1186/1471-2431-14-170

Lavas, J., Slotte, A., Jochym-Nygren, M., van Doorn, J., & Witt-Engerstrom, I. (2006). Communication and eating proficiency in 125 females with Rett syndrome: The Swedish Rett Centre Survey. *Disability and Rehabilitation, 28*(20), 1267-1279. doi: 10.1080/09638280600554868

Lee, J. Y. L., Leonard, H., Piek, J. P., & Downs, J. (2013). Early development and regression in Rett syndrome. *Clinical Genetics, 84*(6), 572-576. doi: 10.1111/cge.12110

Leonard, H. (1996). *Rett syndrome in Australia.* (Master of Public Health), The University of Western Australia, Perth.

Leonard, H., Anderson, A., Bebbington, A., Bao, X., Wong, K., Williams, A., & Downs, J. (2013). Resourceful and creative methods are necessary to research rare disorders. *Developmental Medicine & Child Neurology, 55*(9), 870-871. doi: 10.1111/dmcn.12164

Leonard, H., Colvin, L., Christodoulou, J., Schiavello, T., Williamson, S., Davis, M., . . . Yamashita, Y. (2003). Patients with the R133C mutation: Is their phenotype different from patients with Rett syndrome with other mutations? *Journal of Medical Genetics, 40*(e52), 1-7. doi: 10.1136/jmg.40.5.e52

Leonard, H., Slack-Smith, L., Phillips, T., Richardson, S., D'Orsogna, L., & Mulroy, S. (2004). How can the internet help parents of children with rare neurologic disorders? *Journal of Child Neurology, 19*(11), 902-907.

Lincoln, Y., & Guba, E. (1985). *Naturalistic inquiry*. Newbury Park, CA: SAGE Publications, Inc.

Longobardi, E., Spataro, P., & Rossi-Arnaud, C. (2014). The relationship between motor development, gestures and language production in the second year of life: A mediational analysis. *Infant Behavior & Development, 37*(1), 1-4. doi: 10.1016/j.infbeh.2013.10.002

Louise, S., Fyfe, S., Bebbington, A., Bahi-Biusson, N., Anderson, A., Pineda, M., . . . Leonard, H. (2009). InterRett, a model for international data collection in a rare genetic disorder. *Research in Autism Spectrum Disorders, 3*, 639-659. doi: 10.1016/j.rasd.2008.12.004

Maes, B., Vos, P., & Penne, A. (2010). Analysis of daytime activities for children with profound intellectual and multiple disabilities in specific settings. *The British Journal of Developmental Disabilities, 56*(2), 123-136.

Majnemer, A., & Rosenblatt, B. (1994). Reliability of parental recall of developmental milestones. *Pediatric Neurology, 10*(4), 304-308.

Maljaars, J., Noens, I., Jansen, R., Scholte, E., & van Berckelaer-Onnes, I. (2011). Intentional communication in nonverbal and verbal low-functioning children with autism. *Journal of Communication Disorders, 44*(6), 601-614. doi: 10.1016/j.jcomdis.2011.07.004

Markham, C., van Laar, D., Gibbard, D., & Dean, T. (2009). Children with speech, language and communication needs: their perceptions of their quality of life. *International Journal of Language & Communication Disorders, 44*(5), 748-768. doi: 10.1080/13682820802359892

Marschik, P., Bartl-Pokorny, K., Tager-Flusberg, H., Kaufmann, W. E., Pokorny, F., Grossmann, T., . . . Einspieler, C. (2014). Three different profiles: Early socio-communicative capacities in typical Rett syndrome, the preserved speech variant and normal development. *Developmental Neurorehabilitation, 17*(1), 34-38. doi: 10.3109/17518423.2013.837537

Marschik, P., Einspieler, C., Oberle, A., Laccone, F., & Prechtl, H. (2009). Case report: Retracing atypical development: A preserved speech variant of Rett syndrome. *Journal of Autism and Developmental Disorders, 39*, 958-961. doi: 10.1007/s10803-009-0703-x

Marschik, P., Kaufmann, W., Sigafoos, J., Wolin, T., Zhang, D., Einspieler, C., & Johnston, M. (2013). Changing the perspective on early development in Rett syndrome. *Research in Developmental Disabilities, 34*(4), 1236-1239. doi: 10.1016/j.ridd.2013.01.014

Marschik, P., Kaufmann, W. E., Einspieler, C., Bartl-Pokorny, K., Wolin, T., Pini, G., . . . Sigafoos, J. (2012). Profiling early socio-communicative development in five young girls with the preserved speech variant of Rett syndrome. *Research in Developmental Disabilities, 33*, 1749-1756. doi: 10.1016/j.ridd.2012.04.012

Marschik, P., Pini, G., Bartl-Pokorny, K. D., Duckworth, M., Gugatschka, M., Vollman, R., . . . Einspieler, C. (2012). Early speech-language development in females with Rett syndrome: Focusing on the preserved speech variant. *Developmental Medicine & Child Neurology, 54*, 451-456. doi: 10.1111/j.1469-8749.2012.04123.x

Marschik, P., Sigafoos, J., Kaufmann, W. E., Wolin, T., Talisa, V. B., Bartl-Pokorny, K. D., . . . Einspieler, C. (2012). Peculiarities in the gestural repertoire: An early marker for Rett syndrome? *Research in Developmental Disabilities, 33*, 1715-1721. doi: 10.1016/j.ridd.2012.05.014

Marschik, P., Vollmann, R., Bartl-Pokorny, K. D., Green, V. A., van der Meer, L., Wolin, T., & Einspieler, C. (2014). Developmental profile of speech-language and communicative functions in an individual with the Preserved Speech Variant of Rett syndrome.

Developmental Neurorehabilitation, 17(4), 284-290. doi: 10.3109/17518423.2013.783139

McCormack, J., McLeod, S., Harrison, L., & McAllister, L. (2010). The impact of speech impairment in early childhood: Investigating parents' and speech-language pathologists' perspectives using the ICF-CY. *Journal of Communication Disorders, 43*, 378-396. doi: 10.1016/j.jcomdis.2010.04.009

McLean, L. K., Brady, N., McLean, J. E., & Behrens, G. (1999). Communication forms and functions of children and adults with severe mental retardation in community and institutional settings. *Journal of Speech, Language, and Hearing Research, 42*, 231-240.

McLeod, S., & McCormack, J. (2007). Application of the ICF and ICF-Children and Youth in children with speech impairments. *Seminars in Speech and Language, 28*(4), 254-264.

McLeod, S., & Threats, T. (2008). The ICF-CY and children with communication disabilities. *International Journal of Speech-Language Pathology, 10*(1-2), 92-100.

Merlin, T., Weston, A., & Tooher, R. (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Medical Research Methodology, 9*(1), 34. doi: 10.1186/1471-2288-9-34

Moore, H., Leonard, H., Fyfe, S., De Klerk, N., & Leonard, N. (2005). InterRett - The application of bioinformatics to International Rett syndrome research. *Annals of Human Biology, 32*(2), 228-236. doi: doi:10.1080/03014460500075068

Msall, M., DiGaudio, K., Rogers, B., LaForest, S., Catanzaro, N., Campbell, J., . . . Duffy, L. (1994). The Functional Independence Measure for Children (WeeFIM): Conceptual basis and pilot use in children with developmental disabilities. *Clinical Pediatrics, 33*, 421-430. doi: 10.1177/000992289403300708

Mulhorn, K., & Threats, T. (2008). Speech, hearing, and communication across five national disability surveys: Results of a DISTAB study using the ICF to compare prevalence patterns. *International Journal of Speech-Language Pathology, 10*(1-2), 61-71.

Neul, J., Fang, P., Barrish, J., Lane, J., Caeg, E., Smith, E., . . . Glaze, D. (2008). Specific mutations in Methyl-CpG-Binding Protein 2 confer different severity in Rett syndrome. *Neurology, 70*, 1313-1321. doi: 10.1212/01.wnl.0000291011.54508.aa

Neul, J., Kaufmann, W., Glaze, D., Christodoulou, J., Clarke, A., Bahi-Biusson, N., . . . Percy, A. (2010). Rett syndrome: Revised diagnostic criteria and nomenclature. *Annals of Neurology, 68*(6), 944-950. doi: 10.1002/ana.22124

Neul, J., Lane, J., Lee, H.-S., Geerts, S., Barrish, J., Annese, F., . . . Percy, A. (2014). Developmental delay in Rett syndrome: Data from the natural history study. *Journal of Neurodevelopmental Disorders, 6*(1), 20. doi: 10.1186/1866-1955-6-20

Nielsen, J., Ravn, K., & Schwartz, M. (2001). A 77-year-old woman and a preserved speech variant among the Danish Rett patients with mutations in MECP2. *Brain & Development, 23*, S320-S323.

O'Halloran, R., & Larkins, B. (2008). The ICF Activities and Participation related to speech-language pathology. *International Journal of Speech-Language Pathology, 10*(1-2), 18-26. doi: 10.1080/14417040701772620

Oudgenoeg-Paz, O., Volman, M. J. M., & Leseman, P. P. M. (2012). Attainment of sitting and walking predicts development of productive vocabulary between ages 16 and 28 months. *Infant Behavior & Development, 35*(4), 733-736. doi: 10.1016/j.infbeh.2012.07.010

Owens, R. E. (2012). *Language development: An introduction* (8th ed.). Upper Saddle River: Pearson Education Inc.

Ozonoff, S., Iosif, A.-M., Young, G. S., Hepburn, S., Thompson, M., Colombi, C., . . . Rogers, S. J. (2011). Onset patterns in autism: Correspondence between home video and parent report. *Journal of the American Academy of Child & Adolescent Psychiatry, 50*(8), 796-806. e791.

Palisano, R., Rosenbaum, P., Walter, S., Russel, D., Wood, E. P., & Galuppi, B. (1997). Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine & Child Neurology, 39*(4), 214-223.

Parkes, J., Hill, N., Platt, M., & Donnelly, C. (2010). Oromotor dysfunction and communication impairments in children with cerebral palsy: a register study. *Developmental Medicine & Child Neurology, 52*, 1113-1119. doi: 10.1111/j.1469-8749.2010.03765x

Pence Turnbull, K. L., & Justice, L. M. (2012). *Language development from theory to practice* (2nd ed.). New Jersey: Pearson.

Pizzo, L., & Bruce, S. M. (2010). Language and play in students with multiple disabilities and visual impairments or deaf-blindness. *Journal of Visual Impairment & Blindness, 104*(5), 287-297.

Portney, L., G, & Watkins, M., P. (2009). *Foundations of clinical research: Applications to practice* (3rd ed.). New Jersey: Pearson Education Inc.

Power, E., Anderson, A., & Togher, L. (2011). Applying the WHO ICF framework to communication assessment and goal setting in Huntington's disease: A case discussion. *Journal of Communication Disorders, 44*, 261-275. doi: 10.1016/j.jcomdis.2010.12.004

QRS International Pty Ltd. (2012). NVivo 10 (Version 9).

Raghavendra, P., Bornman, J., Granlund, M., Bjorck-Akesson, E. (2007). The World Healh Organization's International Classification of Functioning, Disability and Health: Implication for clinical and research practice in the field of augmentative and

alternative communication. *Augmentative and Alternative Communication, 23*(4), 349-361. doi: 10.1080/07434610701650928

Ramirez, J.-M., Ward, C. S., & Neul, J. L. (2013). Breathing challenges in Rett Syndrome: Lessons learned from humans and animal models. *Respiratory Physiology & Neurobiology, 189*(2), 280-287. doi: 10.1016/j.resp.2013.06.022

Reichow, B., George-Puskar, A., Lutz, T., Smith, I. C., & Volkmar, F. R. (2015). Brief report: Systematic review of Rett syndrome in males. *Journal of Autism and Developmental Disorders, 45*(10), 3377-3383. doi: 10.1007/s10803-015-2519-1

Renieri, A., Mari, F., Mencarelli, M., Scala, E., Ariani, F., Longo, I., . . . Zappella, M. (2009). Diagnostic criteria for the Zappella variant of Rett syndrome (the preserved speech variant). *Brain & Development, 31*, 208-216. doi: 10.1016/j.braindev.2008.04.007

Roberts, J. E., Mirrett, P., Anderson, K., Burchinal, M., & Neebe, E. (2002). Early communication, symbolic behavior, and social profiles of young males with fragile X syndrome. *American Journal of Speech-Language Pathology, 11*(3), 295-304. doi: 10.1044/1058-0360(2002/034)

Rose, S. A., Djukic, A., Jankowski, J. J., Feldman, J. F., Fishman, I., & Valicenti-McDermott, M. (2013). Rett syndrome: an eye-tracking study of attention and recognition memory. *Developmental Medicine & Child Neurology, 55*(4), 364-371. doi: 10.1111/dmcn.12085

Rowland, C. (2004). Communication Matrix: Especially for parents. Portland, OR: Design to Learn Products.

Rowland, C. (2011). Using the Communication Matrix to assess expressive skills in early communicators. *Communication Disorders Quarterly, 32*(3), 190-201. doi: 10.1177/1525740110394651

Rowland, C., & Fried-Oken, M. (2010). Communication Matrix: A clinical and research assessment tool targeting children with severe communication disorders. *Journal of Pediatric Rehabilitation Medicine: An Interdisciplinary Approach, 3*, 319-329. doi: 10.3233/PRM-2010-0144

Russel, G., Miller, L. L., Ford, T., & Golding, J. (2013). Assessing recall in mothers' retrospective reports: Concerns over children's speech and language development. *Journal of Abnormal Child Psychology*. doi: 10.1007/s10802-013-9819-8

Ryan, D., McGregor, F., Akermanis, M., Southwell, K., Ramke, M., & Woodyatt, G. (2004). Facilitating communication in children with multiple disabilities: three case studies of girls with Rett syndrome. *Disability and Rehabilitation, 26*(21/22), 1286-1277. doi: 10.1080/09638280412331280280

Sabzmakan, L., Mohammadi, E., Morowatisharifabad, M. A., Afaghi, A., Naseri, M. H., & Mirzaei, M. (2014). Environmental determinants of cadiovascular disease risk factors:

A qualitative directed content analysis. *Iranian Red Crescent Medical Journal, 16*(5), e11573. doi: 10.5812/ircmj.11573

Schenker, R., Coster, W. J., & Parush, S. (2005). Neuroimpairments, activity performance, and participation in children with cerebral palsy mainstreamed in elementary schools. *Developmental Medicine & Child Neurology, 12*, 808-814. doi: 10.1017/S0012162205001714

Schwartzman, J. S. (2013). The use of eye-gaze technology in girls with rett syndrome. *Pediatric Neurology, 48*(2), 159-159. doi: http://dx.doi.org/10.1016/j.pediatrneurol.2012.10.007

Sharma, A., & Cockerill, H. (2014). *Mary Sheridan's From Birth to Five Years: Children's Developmental Progress* (4th ed.). Abingdon: Routledge.

Shokoohi-Yekta, M., & Hendrickson, J. M. (2010). Friendships with peers with severe disabilities: American and Iranian secondary students' ideas about being a friend. *Education and Training in Autism and Developmental Disabilities, 45*(1), 23-37.

Sigafoos, J., & Dempsey, R. (1992). Assessing choice making among children with multiple disabilities. *Journal of Applied Behavior Analysis, 25*(3), 747-755. doi: 10.1901/jaba.1992.25-747

Sigafoos, J., Green, V. A., Schlosser, R., O'Eilly, M. F., Lancioni, G. E., Rispoli, M., & Lang, R. (2009). Communication Intervention in Rett Syndrome: A Systematic Review. *Research in Autism Spectrum Disorders, 3*(2), 304-318.

Sigafoos, J., Kagohara, D., van der Meer, L., Green, V. A., O'Reilly, M. F., Lancioni, G. E., . . . Zisimopoulos, D. (2011). Communication Assessment for Individuals with Rett Syndrome: A Systematic Review. *Research in Autism Spectrum Disorders, 5*(2), 692-700.

Sigafoos, J., Laurie, S., & Pennell, D. (1995). Preliminary assessment of choice making among children with Rett syndrome. *Journal of the Association for Persons with Severe Handicaps, 20*(3), 175-184.

Sigafoos, J., Laurie, S., & Pennell, D. (1996). Teaching children with Rett syndrome to request preferred objects using aided communication: two preliminary studies. *Augmentative and Alternative Communication, 12*(2), 88-96.

Sigafoos, J., Woodyatt, G., Keen, D., Tait, K., Tucker, M., Roberts-Pennell, D., & Pittendreigh, N. (2000). Identifying potential communicative acts in children with developmental and physical disabilities. *Communication Disorders Quarterly, 21*, 77-86.

Sigafoos, J., Woodyatt, G., Tucker, M., Roberts-Pennell, D., & Pittendreigh, N. (2000). Assessment of potential communicative acts in three individuals with Rett syndrome. *Journal of Developmental and Physical Disabilities, 12*(3), 203-216.

Simeonsson, R. J. (2003). Classification of communication disabilities in children: contribution of the International Classification on Functioning, Disability and Health. *International Journal of Audiology, 42*, S2-S8.

Simeonsson, R. J., Bjorck-Akesson, E., & Lollar, D. J. (2012). Communication, disability, and the ICF-CY. *Augmentative and Alternative Communication, 28*(1), 3-10. doi: 10.3109/07434618.2011.653829

Skene, P., Illingworth, R., Webb, S., Kerr, A., James, K., Turner, D., . . . Bird, A. (2010). Neuronal MeCP2 is expressed at near histone-octamer levels and globally alters the chromatin state. *Molecular Cell, 37*, 457-468. doi: 10.1016/j.molcel.2010.01.030

Skotko, B. G., Koppenhaver, D. A., & Erickson, K. A. (2004). Parent Reading Behaviors and Communication Outcomes in Girls with Rett Syndrome. *Exceptional Children, 70*(2), 145.

Sparrow, S., Balla, D., & Cicchetti, D. (1984). Vineland adaptive behavior scale. Minnesota: American Guidance Service Inc.

Speech Pathology Australia. (n.d.). Augmentative and alternative communication. Retrieved 10 September 2016, from https://www.speechpathologyaustralia.org.au/spaweb/Document_Management/Public/Fact_Sheets.aspx#anchor_aac

Stasolla, F., De Pace, C., Damiani, R., Di Leone, A., Albano, V., & Perilli, V. (2014). Comparing PECS and VOCA to promote communication opportunities and to reduce stereotyped behaviors by three girls with Rett syndrome. *Research in Autism Spectrum Disorders, 8*(10), 1269-1278. doi: 10.1016/j.rasd.2014.06.009

Stasolla, F., Perilli, V., Di Leone, A., Damiani, R., Albano, V., Stella, A., & Damato, C. (2015). Technological aids to support choice strategies by three girls with Rett syndrome. *Research in Developmental Disabilities, 36*, 36-44. doi: 10.1016/j.ridd.2014.09.017

StataCorp LP. (2011). STATA (Version 12). College Station, Texas.

Stephenson, J., & Dowrick, M. (2005). Parents' perspectives on the communication skills of their children with severe disabilities. *Journal of Intellectual & Developmental Disability, 30*(2), 75-85. doi: 10.1080/13668250500125031

Tait, K., Sigafoos, J., Woodyatt, G., O'Reilly, M., & Lancioni, G. (2004). Evaluating parent use of functional communication training to replace and enhance prelinguistic behaviours in six children with developmental and physical disabilities. *Disability and Rehabilitation, 26*(21-22), 1241-1254. doi: doi:10.1080/09638280412331280253

Tams-Little, S., & Holdgrafer, G. (1996). Early communication development in children with Rett syndrome. *Brain & Development, 18*(5), 376-378.

The Rett Syndrome Diagnostic Criteria Working Group. (1988). Diagnostic criteria for rett syndrome. *Annals of Neurology, 23*(4), 425-428. doi: 10.1002/ana.410230432

Townend, G. S., Bartl-Pokorny, K., Sigafoos, J., Curfs, L. M. G., Bölte, S., Poustka, L., . . . 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

Townend, G. S., Marschik, P., Smeets, E. E. J., van de Berg, R., van de Berg, M., & Curfs, L. M. G. (2015). 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*. doi: 10.1007/s10882-015-9455-z

Uchino, J., Suzuki, M., Hoshino, K., Nomura, Y., & Segawa, M. (2001). Development of language in Rett syndrome. *Brain & Development, 23*(Supplement 1), S233-S235. doi: 10.1016/S0387-7604(01)00367-9

United Nations. (2006). *United Nations Convention on the Rights of Persons with Disabilities*. New York: United Nations.

United Nations Economic and Social Commission for Asia and the Pacific. (2012). *Incheon Strategy to "Make the Right Real" for Persons with Disabilities in Asia and the Pacific.* Bangkok: United Nations.

Urbanowicz, A., Downs, J., Girdler, S., Ciccone, N., & Leonard, H. (2014). Aspects of speech-language abilities are influenced by MECP2 mutation type in girls with Rett syndrome. *American Journal of Medical Genetics Part A, 9999*, 1-9. doi: 10.1002/ajmg.a.36871

Urbanowicz, A., Downs, J., Girdler, S., Ciccone, N., & Leonard, H. (in press). An exploration of the use of eye gaze and gestures in females with Rett syndrome. *Journal of Speech, Language, and Hearing Research*.

Urbanowicz, A., Leonard, H., Girdler, S., Ciccone, N., & Downs, J. (2016). Parental perspectives on the communication abilities of their daughters with Rett syndrome. *Developmental Neurorehabilitation, 19*(1), 17-25. doi: 10.3109/17518423.2013.879940

Van Acker, R., & Grant, S. (1995). An effective computer-based requesting system for persons with Rett syndrome. *Journal of Childhood Communication Disorders, 16*(2), 31-38.

van der Schuit, M., Segers, E., van Balkom, H., & Verhoeven, L. (2011). Early Language Intervention for Children with Intellectual Disabilities: A Neurocognitive Perspective. *Research in Developmental Disabilities, 32*(2), 705-712.

Velloso, R. L., Araυjo, C. A., & Schwartzman, J. S. (2009). Concepts of color, shape, size and position in ten children with Rett syndrome. *Arquivos de Neuro-Psiquiatria, 67*(1), 50-54. doi: 10.1590/S0004-282X2009000100013

Vignoli, A., Fabio, R., La Briola, F., Giannatiempo, S., Antonietti, A., Maggiolini, S., & Canevini, M. (2010). Correlations between neurophysiological, behavioral, and cognitive function in Rett syndrome. *Epilepsy & Behavior, 17*, 489-496. doi: 10.1016/j.yebeh.2010.01.024

Walker, E. M., Crawford, F., & Leonard, H. (2014). Community participation: Conversations with parent-carers of young women with Rett syndrome. *Journal of Intellectual and Developmental Disability, 39*(3), 243-252. doi: 10.3109/13668250.2014.909919

Wandin, H., Lindberg, P., & Sonnander, K. (2015). Communication intervention in Rett syndrome: a survey of speech language pathologists in Swedish health services. *Disability and Rehabilitation, 37*(15), 1324-1333. doi: 10.3109/09638288.2014.962109

Wang, M. V., Lekhal, R., Aarø, L. E., & Schjølberg, S. (2014). Co-occurring development of early childhood communication and motor skills: results from a population-based longitudinal study. *Child: Care, Health and Development, 40*(1), 77-84. doi: 10.1111/cch.12003

Watt, N., Wetherby, A. M., & Shumway, S. (2006). Prelinguistic predictors of language outcomes at 3 years of age. *Journal of Speech, Language, and Hearing Research, 49*, 1224-1237. doi: 10.1044/1092-4388(2006/088)

Weaving, L. S., Williamson, S. L., Bennetts, B., Davis, M., Ellaway, C. J., Leonard, H., . . . Christodoulou, J. (2003). Effects of MECP2 mutation type, location and X-inactivation in modulating Rett syndrome phenotype. *American Journal of Medical Genetics Part A, 118*(2), 103-114. doi: 10.1002/ajmg.a.10053

Wetherby, A. M., Allen, L., Cleary, J., Kublin, K., & Goldstein, H. (2002). Validity and reliability of the Communication and Symbolic Behavior Scales Developmental Profile with very young children. *Journal of Speech, Language, and Hearing Research, 45*, 1202-1218. doi: 10.1044/1092-4388(2002/097)

Wetherby, A. M., & Prizant, B. (2002). Communication and Symbolic Behavior Scales Developmental Profile. Baltimore, MD: Paul H. Brookes Publishing Co., Inc.

Wigram, T., & Lawrence, M. (2005). Music therapy as a tool for assessing hand use and communicativeness in children with Rett syndrome. *Brain & Development, 27*, S95-S96. doi: 10.1016/j.braindev.2005.03.019

Woodyatt, G., & Ozanne, A. (1992). Communication abilities and Rett syndrome. *Journal of Autism and Developmental Disorders, 22*(2), 155-173.

Woodyatt, G., & Ozanne, A. (1993). A longitudinal study of cognitive skills and communication behaviours in children with Rett syndrome. *Journal of Intellectual Disability Research, 37*, 419-435.

Woodyatt, G., & Ozanne, A. (1994). Intentionality and communication in four children with Rett syndrome. *Australia and New Zealand Journal of Developmental Disabilities, 19*(3), 173-183.

World Health Organization. (2007). *International Classification of Functioning, Disability and Health: Children & Youth Version* (1st ed.). Geneva: World Health Organization.

World Health Organization, & The World Bank. (2011). *Word Report on Disability*. Geneva: World Health Organization.

World Health Organization. (2001). *International Classification of Classification of Functioning, Disability and Health*. Geneva: World Health Organization.

Yamashita, Y., Kondo, I., Fukuda, T., Morishima, R., Kusaga, A., Iwanaga, R., & Matsuishi, T. (2001). Mutation analysis of the methyl-CpG-binding protein 2 gene (MECP2) in Rett patients with preserved speech. *Brain & Development, 23*, S157-S160.

Yasuhara, A., & Sugiyama, Y. (2001). Music therapy for children with Rett syndrome. *Brain & Development, 23*, S82-S84.

Zampini, L., & D'Odorico, L. (2009). Communicative gestures and vocabulary development in 36-month-old children with Down's syndrome. *International Journal of Language & Communication Disorders, 44*(6), 1063-1073. doi: 10/3109/1368280802398288

Zappella, M. (1992). The Rett girls with preserved speech. *Brain & Development, 14*, 98-101.

Zappella, M. (1994). Rett syndrome-like hand-washing, developmental arrest and autistic symptoms in two Italian girls. *European Child & Adolescent Psychiatry, 3*(1), 52-56.

Zappella, M. (1997). The preserved speech variant of the Rett complex: a report of 8 cases. *European Child & Adolescent Psychiatry, 6*, 23-25.

Zappella, M., Gillberg, C., & Ehlers, S. (1998). The preserved speech variant: A subgroup of the Rett complex: A clinical report of 30 cases. *Journal of Autism and Developmental Disorders, 28*(6), 519-526.

Ziviani, J., Feeney, R., Rodger, S., & Watter, P. (2010). Systematic review of early intervention programmes for children from birth to nine years who have a physical disability. *Australian Occupational Therapy Journal, 57*(4), 210-223. doi: 10.1111/j.1440-1630.2010.00850.x

Zwaigenbaum, L., Bryson, S., & Garon, N. (2013). Early identification of autism spectrum disorders. *Behavioural Brain Research, 251*, 133-146. doi: 10.1016/j.bbr.2013.04.004

Appendix A: Literature review data extraction form

Study Identification	
APA citation	
Location(s) of the study	
Aim of study	
Study just on communication?	
Factors	
Communication outcome/s	
Participants	
Diagnosis confirmed?	
MECP2?	
N=	
Age	
Co-morbidities	
Study design	
Level of evidence (NHMRC)	
Type of design	
Methods	
Communication assessment procedures • What communication skills were assessed? • What factors influencing communication (i.e. apraxia) were assessed? • How were skills & factors assessed (i.e. parent interview, observations, standardised assessment)	
Goal/s for intervention	
Intervention procedures	
Data analysis	
Conclusions	
Strengths	
Limitations	
Clinical practice & Future research	

Appendix B: Participant information sheet and consent form

PARENT INFORMATION SHEET
"Understanding communication in Rett syndrome"

Why are we doing this study?
A variety of factors influence communication in Rett syndrome, however many of these remain poorly understood. This study is part of a larger doctoral study and aims to understand how girls of different ages communicate. Findings from this study will help us understand more about communication in Rett syndrome and help us to develop a specific way to measure communication.

Why was I invited to participate in this study?
You have been invited to participate in this specific project because you are the mother of a daughter with Rett syndrome and your family is already contributing to the Australian Rett Syndrome Database.

What will I be asked to do if I decide to take part in this study?
You will be asked to participate in a face-to-face or telephone interview to talk about your daughter's communication which will take approximately 45 minutes to 1 hour. Interviews can be completed in two sittings if you would like. If you agree to take part in this study, we will contact you to arrange a suitable time and place for the interview. During the interview, you will be asked about how your daughter communicates with others and what factors you believe make is easier or harder for her to communicate. We will record the interview and type it out word for word afterwards. After the interview we will send you a copy of the interview transcript if you like. This will give you the chance to explain further or add more details to your responses.

What are the possible risks and/or discomforts?
We do not envisage any risks or side-effects from participating in this study. You do not have to answer any questions you do not feel comfortable with. This study will involve some of your time but we anticipate that that would be small.

What about my privacy?
No names or identifying information will ever be released. Names and contact information are stored separately from the information recorded during interviews. Your interview will only be identifiable by your Australian Rett Syndrome Database unique identification number. Interviews will be digitally recorded and transcribed word for word. All digital information will be stored on a secure network at the Telethon Institute of Child Health Research, Perth. Research findings that are published will be in a form that does not allow identification of any person taking part in this study.

Do I have to take part?
Participation in this study is entirely voluntary and you may withdraw your consent to participate at any time without penalty.

Who has approved this study?
This study has been approved by Edith Cowan University, Perth.

Who to contact if you have concerns about the organisation or running of this study?
If you have any concerns or complaints regarding this study, please contact Dr. Sonya Girdler on (08) 6304 3582 or 0448913066.

Who to contact for more information about this study:
This study will be conducted by the doctoral candidate, Anna Urbanowicz under the supervision of the Chief Investigator of the Australian Rett Syndrome Database, Dr. Helen Leonard and supervisors Dr. Jenny Downs and Dr. Sonya Girdler. This study is being undertaken in collaboration with Edith Cowan University, Western Australia and the Telethon Institute for Child Health Research, Western Australia. If you would like any more information about this study, please do not hesitate to contact the Chief Investigator or the interviewer who would be very happy to answer your questions.

Chief Investigator
Dr. Helen Leonard
(08) 9489 7790
hleonard@ichr.uwa.edu.au

Interviewer
Anna Urbanowicz
(08) 9489 7786
aurbanowicz@ichr.uwa.edu.au

What to do next if you would like to take part in this research:
If you would like to be involved in this research study, plead read, sign and return the consent form in the provided envelope or scan the completed consent form and send to as an attachment to aussierett@ichr.uwa.edu.au

THANK YOU FOR YOUR TIME

PLEASE RETAIN A COPY OF THIS INFORMATION SHEET FOR YOUR RECORDS

CONSENT FORM

"Understanding communication in Rett syndrome"

I ..... have read
Given Names Surname

the information sheet explaining the study entitled "Understanding communication in Rett syndrome."

I have read and understood the information given to me. Any questions I have asked have been answered to my satisfaction.

I agree to participate in the study and understand:

- That I may withdraw my consent at any time without penalty;
- All provided information is treated as strictly confidential and will not be released by the investigator;
- What data is being collected, what the purpose is, and what will be done with the data upon completion of the research; &
- Data gathered from the results of this study may be published, provided that names are not used.

Participant Signature .....

Date .....

I, ... have explained the above to the
(Investigator's full name)

signatory who stated that she understood the same.

Investigator Signature .....

Date .....

Appendix C: Interview guide

Receptive communication

1. Does your daughter understand spoken messages?
2. Does your daughter understand nonverbal messages?
3. Does your daughter understand formal sign language?
4. Does your daughter read?
5. Do you have any other comments about how your daughter understands?

Expressive communication

Form

1. Does your daughter speak or use vocalisations?
2. Does your daughter use any communication devices, facilitated communication, or other programs to communicate?
3. In what other ways does your daughter communicate?
4. Does your daughter draw or write?

Function

1. How does your daughter let you know she wants something?
2. How does your daughter let you know her choices?
3. How does your daughter let you how she is feeling?
4. Does your daughter try and get your attention to show you something?
5. Do you have any other comments about how your daughter communicates?

Social interactions

6. Does your daughter engage in conversation?

Factors influencing communication

1. What motivates your daughter to communicate?
2. What things make it easier/harder for your daughter to understand?
3. What things make it easier/harder for your daughter to communicate her messages?
4. What things make it easier/harder for your daughter to engage in conversation?
5. Do you have any other comments about things that make it easier or harder for your daughter to communicate?
6. Have her communication skills changed at all?
7. Does your daughter receive speech therapy?

Other

1. Do you have any other comments you would like to share or questions you would like to ask?

Appendix D: Edith Cowan University Human Research Ethics Approval

Dear Anna

Project 7455 URBANOWICZ
Communication: How do females with Rett syndrome perform this activity?

Student Number: 10044451

The ECU Human Research Ethics Committee (HREC) has reviewed your application and has granted ethics approval for your research project. In granting approval, the HREC has determined that the research project meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

The approval period is from 31 October 2011 to 8 June 2014.

The Research Assessments Team has been informed and they will issue formal notification of approval. Please note that the submission and approval of your research proposal is a separate process to obtaining ethics approval and that no recruitment of participants and/or data collection can commence until formal notification of both ethics approval and approval of your research proposal has been received.

All research projects are approved subject to general conditions of approval. Please see the attached document for details of these conditions, which include monitoring requirements, changes to the project and extension of ethics approval.

Please feel free to contact me if you require any further information.

Regards
Kim

Kim Gifkins
Research Ethics Officer
Edith Cowan University
270 Joondalup Drive
JOONDALUP WA 6027
Phone: (08) 6304 2170
Fax: (08) 6304 5044
Email: research.ethics@ecu.edu.au

Hi Anna

Project Number: 7455 URBANOWICZ
Project Name: Communication: How do females with Rett syndrome perform this activity?

Thank you for your Annual Ethics Report, our records have been updated to reflect the information provided.

Your request for an extension of ethics approval for this project has been granted until 15 August 2016.

Kind regards

Rowe

Rowe Oakes
Ethics Support Officer
Office of Research & Innovation, Edith Cowan University
Phone: +61 08 6304 2943
Email: research.ethics@ecu.edu.au
www.ecu.edu.au/research | [facebook.com/research.ecu]facebook.com/research.ecu

Appendix E: Princess Margaret Hospital for Children Human Research Ethics Approval for the ARSD

Government of **Western Australia**
Department of **Health**
Child and Adolescent Health Service

PMH 100 CENTENARY 1909-2009

Dr Madhur Ravikumara
C/- Dr Helen Leonard
Telethon Institute for Child Health Research
100 Roberts Road
SUBIACO WA 6008

Dear Drs Ravikumara and Leonard

REGISTRATION NO:	**1909/EP**
TITLE:	**Towards evidence-based care of Rett syndrome: A research model to inform management of rare disorders**
MEETING DATE:	**19 May 2011**

RGO and Ethics requirements satisfied 2 June 2011

The Princess Margaret Hospital for Children Ethics Committee and the Research Governance Office consider that the study protocol conforms to the requirements of the NHMRC *Statement on Ethical Conduct in Human Research (National Statement)* and resolved at the meeting to recommend the protocol for approval to the Chief Executive. This recommendation has been ratified by the Child and Adolescent Health Service.

The Ethics Committee does however wish to be informed immediately of:

I. any untoward effects experienced by any participant in the trial where those effects in degree or nature were not anticipated by the researchers, and steps taken to deal with these,

II. substantial changes in the research protocol together with an indication of ethical implications, and

III. other unforseen events.

The Ethics Committee has been charged with the responsibility of keeping the progress of all approved research under surveillance. A copy of the final result must be forwarded to the Committee upon completion of the research or if the research is not completed within twelve months you are asked to submit a progress report and annually thereafter. This information should include:

Princess Margaret Hospital for Children
Roberts Road Subiaco WA 6008
GPO Box D184 Perth WA 6840
Tel: (08) 9340 8222 Fax: (08) 9340 8111
www.cahs.health.wa.gov.au
wa.gov.au

a) The status of the project (completed/in progress/abandoned/not commenced). In the event that a project does not commence within 12 months of being approved by the Ethics Committee the study must be resubmitted to the Committee for approval.

b) Compliance with conditions of ethical approval, including security of records and procedures for consent.

c) Compliance with any special conditions stated by the Ethics Committee as a condition of approval.

d) Results from the study to date, including outcome.

Please note that approval for studies is for **three years** and if the research is not completed within that period of time, a request for an extension of time should be submitted for consideration. In the event that a project does not commence within **12 months** of being approved by the Ethics Committee, the study must be resubmitted to the Committee for approval.

In accordance with the NHMRC National Statement on Ethical Conduct in Human Research Chapter 5.5.3, researchers have a significant responsibility in monitoring and must submit the following to the Ethics Committee:

- Annual Reports on the anniversary of the approval date of the study
- Adverse event reports as received
- Amendments and extensions to the study to be requested in adequate time

Please quote the above registration number on all correspondence.

Yours sincerely

[redacted]

Dr Mark Salmon
Executive Director
Medical Services

2 June 2011

- **The Ethics Committee is constituted, and operates in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Research Involving Humans**

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cc:

Government of **Western Australia**
Department of **Health**
Child and Adolescent Health Service

Our Ref: 1909EP

From: PMH, Ethics <pmhethics@health.wa.gov.au>

To: madhur.ravikumara@health.wa.gov.au

cc: hleonard@ichr.uwa.edu.au; margaret.thomson@health.wa.gov.au

Subject: 1909EP - EXTENSION OF TRIAL APPROVAL

Dear Dr Ravikumara

HUMAN RESEARCH ETHICS COMMITTEE (HREC)

HREC Ref	**1909EP**
Study Expiry Date	**19/05/2017**
Study Title	**Towards evidence-based care of Rett syndrome: A research model to inform management of rare disorders**

The Princess Margaret Hospital for Children Ethics Committee has recommended approval of the extension application of this study. This recommendation has been ratified and confirmed by the Child and Adolescent Health Service.

It should be noted that all other aspects of the approval remain unchanged. This is so, in particular, in relation to the progress reports required, as in National Statement S5.5 & S5.7.1, and regarding any further amendments to the protocols.

Please do not hesitate to contact me if you have any queries in regards to this study. Please quote the above study number 1909EP on all correspondence associated with this study.

Yours sincerely

HREC Administration
25/08/2015

Appendix F: Princess Margaret Hospital for Children Human Research Ethics Approval for InterRett

Government of **Western Australia**
Department of **Health**
Child and Adolescent Health Service

PMH 100 CENTENARY 1909-2009

Dr Helen Leonard
Telethon Institute for Child Health Research
100 Roberts Road
SUBIACO WA 6009

Dear Dr Leonard

REGISTRATION NUMBER:	**880/EP**
TITLE:	**InterRett-IRSA Rett Phenotype Database**
MEETING DATE:	**20 August 2009**

The Princess Margaret Hospital for Children Ethics Committee has recommended approval of a 3 year extension to this study. **This extension will expire on 19 June 2012.** This recommendation has been ratified and confirmed by the Child and Adolescent Health Service.

It should be noted that all other aspects of the approval remain unchanged. This is so, in particular, in relation to the progress reports required and regarding any further amendments to the protocols.

Please quote the above registration number on all correspondence.

Yours sincerely

[redacted]

Dr Mark Salmon
Executive Director
Medical Services

27 August 2009

- **The Ethics Committee is constituted, and operates in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Research Involving Humans**

Princess Margaret Hospital for Children
Roberts Road Subiaco WA 6008
GPO Box D184 Perth WA 6840
Tel: (08) 9340 8222 Fax: (08) 9340 8111
www.cahs.health.wa.gov.au
wa.gov.au

Government of **Western Australia**
Department of **Health**

Child and Adolescent Health Service

PMH 100 CENTENARY 1909-2009

Dr Helen Leonard
Telethon Institute for Child Health Research
100 Roberts Road
SUBIACO WA 6008

Dear Dr Leonard

REGISTRATION NUMBER:	**880/EP**
TITLE:	**InterRett-IRSA Rett Phenotype Database (follow on from 785/EP)**
MEETING DATE:	**20 September 2012**

The Princess Margaret Hospital for Children Ethics Committee has recommended approval of a 3 year extension to this study. **This extension will expire on 19 June 2015**. This recommendation has been ratified and confirmed by the Child and Adolescent Health Service.

It should be noted that all other aspects of the approval remain unchanged. This is so, in particular, in relation to the progress reports required and regarding any further amendments to the protocols.

Please quote the above registration number on all correspondence.

Yours sincerely

[redacted]

Dr Mark Salmon
Executive Director
Medical Services

27 September 2012

- **The Ethics Committee is constituted, and operates in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Research Involving Humans**

LetSept12Amend.doc

Princess Margaret Hospital for Children
Roberts Road Subiaco WA 6008
GPO Box D184 Perth WA 6840
Tel: (08) 9340 8222 Fax: (08) 9340 8111
www.cahs.health.wa.gov.au
wa.gov.au

THE UNIVERSITY OF WESTERN AUSTRALIA

Human Ethics
Office of Research Enterprise
The University of Western Australia
M459, 35 Stirling Highway
Crawley WA 6009 Australia
T +61 8 6488 4703 / 3703
F +61 8 6488 8775
E humanethics@uwa.edu.au
CRICOS Provider Code: 00126G

Our Ref: RA/4/1/7449 08 May 2015

Dr Helen Leonard
UWA Centre for Child Health Research
MBDP: M560

Dear Doctor Leonard

HUMAN RESEARCH ETHICS APPROVAL - THE UNIVERSITY OF WESTERN AUSTRALIA

The InterRett database: Looking Back and Looking Forward

Student(s):

Ethics approval for the above project has been granted in accordance with the requirements of the *National Statement on Ethical Conduct in Human Research* (National Statement) and the policies and procedures of The University of Western Australia. Please note that the period of ethics approval for this project is five (5) years from the date of this notification. However, ethics approval is conditional upon the submission of satisfactory progress reports by the designated renewal date. Therefore initial approval has been granted from 08 May 2015 to 01 May 2016.

You are reminded of the following requirements:

1. The application and all supporting documentation form the basis of the ethics approval and you must not depart from the research protocol that has been approved.
2. The Human Ethics office must be approached for approval in advance for any requested amendments to the approved research protocol.
3. The Chief Investigator is required to report immediately to the Human Ethics office any adverse or unexpected event or any other event that may impact on the ethics approval for the project.
4. The Chief Investigator must submit a final report upon project completion, even if a research project is discontinued before the anticipated date of completion.

Any conditions of ethics approval that have been imposed are listed below:

Special Conditions

None specified

The University of Western Australia is bound by the *National Statement* to monitor the progress of all approved projects until completion to ensure continued compliance with ethical principles.

The Human Ethics office will forward a request for a Progress Report approximately 30 days before the due date.

If you have any queries please contact the Human Ethics office at humanethics@uwa.edu.au.

Please ensure that you quote the file reference – RA/4/1/7449 – and the associated project title in all future correspondence.

Yours sincerely

[redacted]

Dr Caixia Li
Manager, Human Ethics

Appendix G: Example completed video coding framework

Name	Video year	Time to choice (secs)	Description				Communication partner				Girl/woman with Rett syndrome			Choice making outcome		
			Choice items	Setting	Who	Are they behind the camera	Time	Behaviour code	Behaviour details	Position	Time	Behaviour code	Behaviour details	Choice	Did partner recognise choice	Outcome justification
Ava[a]	2014	6	2 foods	Ava is at home. Both items are placed in front of X on table. TV is playing in background.	Mum	No	19:03-19:04	Language	"Do you want ravioli?"	Sitting on kitchen chair at table	19:09	Early sounds	Vocalises	Yes	Yes at same time as coder	Choice was indicated via gesture, eye gaze & sounds
							19:03-19:04	Gestures	Holds up bowl of ravioli		19:09-19:10	Gestures	Touches bowl of ravioli			
							19:05-19:06	Language	"Or spaghetti?"		19:09	Eye gaze	Looks at ravioli			
							19:05-19:06	Gestures	Places down bowl of ravioli & holds up spaghetti in front of X.							
							19:07-19:08	Language	"Which one? Which one?							

[a] Pseudonym has been used