

**THE BEHAVIOURAL PHENOTYPE AND THE SUPPORT NEEDS OF GIRLS  
AND WOMEN WITH RETT SYNDROME AND THEIR FAMILIES**

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To Chris and Letizia

## Summary

The study was designed to (i) investigate the behavioural characteristics of individuals with Rett syndrome and (ii) the impact that severity of behavioural and clinical symptoms has on family well-being. A cross-sectional study was conducted to assess differences in behavioural characteristics within subjects and across groups with rare genetic syndromes using standardised measurements. The sample was followed-up after 16 months to examine developmental changes.

Three studies were conducted: a national survey of individuals with Rett syndrome and their families, direct behavioural observation of 11 individuals with Rett syndrome in the natural environment and a longitudinal follow-up of the national survey.

Results confirmed that behaviours such as hand stereotypies, breathing abnormalities and sleep disturbances are typical of the syndrome. Other behaviours, such as autistic features, impulsivity and overactivity, self-injurious behaviour and depression were also investigated. Although the behaviours were reported in some of the participants, these were not typical of the syndrome. Although some trends were highlighted in the analysis of the longitudinal study, the behavioural features of the group were found to be stable over time.

Family stress, anxiety and depression were found to be related to increased severity in areas such mood, fear/anxiety, body rocking and expressionless face and not related to the severity of the clinical phenotype. Results of the longitudinal family study were consistent with the cross-sectional study in that increased severity of behavioural problems is linked to worse maternal psychological well-being.

Behaviours mostly seen in the group who were observed were: hand stereotypies, breathing abnormalities and self-injurious behaviours. Hand stereotypies were very frequent for the vast majority of the participants. However, analysis suggested that these stereotypies were less frequent when the girls/women were engaged in another activity using the hands. Breathing abnormalities were observed in the younger girls and the behaviour tended to attract adult attention.

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# CHAPTER 1

## INTRODUCTION

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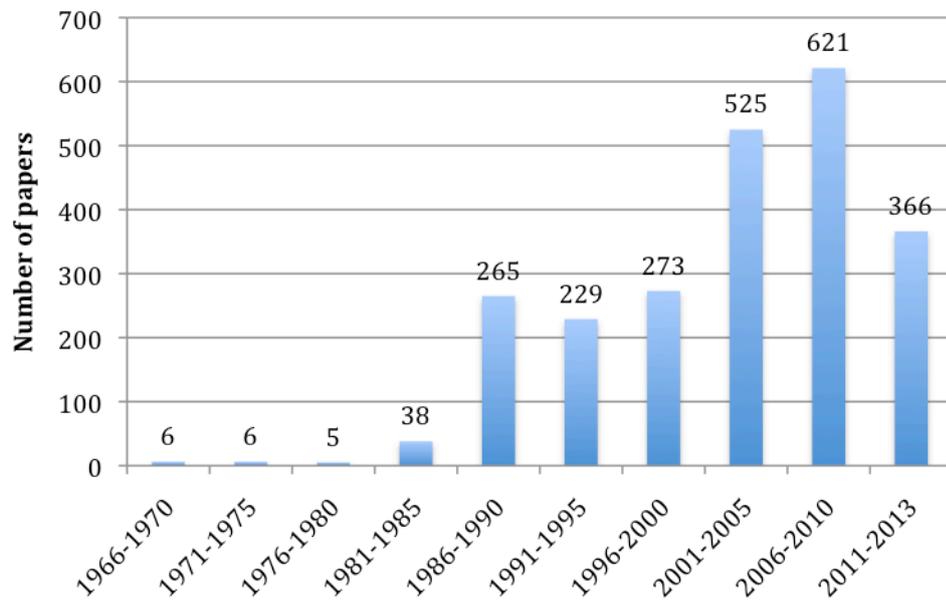
### 1.1 Introduction

One of the first medical accounts of Rett syndrome was by Dr Andreas Rett, a pediatrician in Vienna in 1954. He noticed two girls in his waiting room with similar repetitive hand movements. After checking with his nurse, he discovered other girls showing similar repetitive movements with the hands and with other similar characteristics. At the same time in Sweden, Dr Bengt Hagberg was collecting medical records of girls with similar clinical and behavioural characteristics.

Dr Andreas Rett published his findings in several German journals in 1966. Even though he published a description of the disorder in English 10 years later, his findings remained unrecognised by the English speaking medical community for another 20 years. In 1983, an article on Rett syndrome appeared in the *Annals of Neurology* written by Dr Bengt Hagberg and his colleagues, which finally raised awareness of Rett syndrome. In 1999, Ruthie Amir discovered the gene responsible for Rett syndrome (Amir et al. 1999), a mutation in the methyl-CpG binding protein-2 (MeCP2) gene, located on the X chromosome at Xq28.

Between 1966 and 2013, over 2000 articles have been published in English and other languages on Rett syndrome (RTT) (see Figure 1.1). As can be seen, there has been a dramatic increase in the literature since the Hagberg paper in the early 1980s.

**Figure 1.1 Number of articles published on RTT since 1966 (PubMed source)**



## **1.2 Aim of the study**

The study was designed to (i) investigate the behavioural characteristics of individuals with RTT and (ii) the impact that severity of behavioural and clinical symptoms has on family well-being. The emphasis is on accurate description of behavioural and emotional features of RTT and differences in behavioural characteristics within subjects and across groups with rare genetic syndromes.

The study is divided into 3 parts:

1. A national survey of individuals with RTT and their families
2. Direct behavioural observation of individuals with RTT in the natural environment
3. A longitudinal follow-up of the national survey.

### *1.2.1 The National Survey*

The survey was designed to investigate the following aspects of RTT:

1. The behavioural and emotional features of RTT
2. Behavioural differences within subjects (e.g., across age groups, severity categories, genetic categories)
3. Behavioural differences between RTT and individuals with other rare genetic syndromes controlled for gender and developmental level
4. The impact that severity of behavioural and clinical presentation has on family stress and mental health.

### *1.2.2 Behavioural observation*

Systematic behavioural observation in the natural environment of a sub-sample of individuals with a positive *MECP2* mutation was designed to:

1. Explore the organization of the behavioural repertoire in individuals with RTT
2. Investigate the possible environmental maintenance of the behavioural phenotype associated with RTT
3. Identify optimal environmental conditions for the delivery of care.

### *1.2.3 The Longitudinal Follow-up*

The longitudinal follow-up was designed to investigate changes over time in the behavioural presentation of individuals completing the initial survey and well-being of their families.

## **1.3 Overview of the chapters**

This thesis is divided into 5 parts. The first part includes four introductory chapters, including this first chapter, which sets the scene. Chapter 2 introduces the concept of a behavioural phenotype. Chapter 3 discusses the clinical and genetic characteristics of

RTT and recent research into phenotype - genotype association. Chapter 4 reviews the literature on the behavioural phenotype of RTT.

The second part concerns the national survey. Chapter 5 sets out the research aims of the survey and describes its methodology. Chapter 6 describes the demographic and clinical characteristics of the sample. Chapters 7, 8 and 9 present the results of the national survey. Chapter 7 presents a description of the behavioural and emotional characteristics of the RTT sample. Chapter 8 compares the RTT sample to a well-matched control group of individuals with different rare genetic syndromes on a variety of behavioural measures. Chapter 9 covers the data on family psychological well-being its association with the severity of clinical and behavioural presentation of the individual with RTT.

The third part is a single chapter (Chapter 10), which describes the methodology and results of the longitudinal follow-up.

The fourth part is another single chapter (Chapter 11), which describes the methodology and results of the behavioural observation.

Finally, in the fifth part, Chapter 12 summarises and discusses the findings of the studies undertaken and suggests possible directions for future research.

**CHAPTER 2**  
**BEHAVIOURAL PHENOTYPE**

---

**2.1 Introduction**

Intellectual Disability (ID) has been recognised since antiquity, but it was not until the 19<sup>th</sup> century that the importance of differences in aetiology was recognised. Since mid-way through the 20<sup>th</sup> century, ID has been diagnosed primarily by the level of intellect as measured by the intelligence quotient (IQ), with deficits in adaptive skills, in terms of social, communication and other functional abilities, as another necessary condition (AAIDD 2010). Although severity of ID is categorised according to IQ level (e.g., as mild, moderate, severe or profound as in ICD-10 or DSM IV – see Table 2.1), the emphasis on there being concurrent deficits in adaptive behaviour may explain the lower proportion of the population being recognized as having ID compared to the 2.5% who might be predicted to have an IQ under 70. Prevalence of ID has been found to vary across studies possibly due to differences in study design, methodology and definitions employed. In general an overall rate of 1-2.5% is reported (Gillberg 2003).

**Table 2.1 ICD-10 and DSM-IV Classification of Intellectual Disability based on IQ**

	<b>ICD-10</b>	<b>DSM-IV</b>
Mild	IQ 50-70	IQ 50-55 to 70
Moderate	IQ 35-49	35-40 to 50-55
Severe	IQ 20-34	IQ 20-25 to 35-40
Profound	<20	<20 or 25

Aetiology of ID can be divided into bio-pathological or unspecified origins (Stromme and Hagberg 2000), with the former accounting for the majority. Aetiological factors can be traced to prenatal (genetic or acquired), perinatal (intrauterine or neonatal disorder) or postnatal (infection, brain injury, malnutrition) occurrences. Stromme and Hagberg (2000) reported that 59% of children identified with ID in Norway had an ID with prenatal aetiology, of which 60% had a genetic origin. Moreover, most of these children had a diagnosis of severe ID (70%). Such results are consistent with findings reported elsewhere. A genetic cause was reported in 50.9% of a population studied in Finland (Arvio and Sillanpaa 2003). In a study to explore the consequences of late diagnosis of a group of adults with ID in Italy, Verri et al. (2004) reported that prenatal aetiology was detected in 34% of patients with mild ID and 28% of patients with severe ID. A review by Aicardi (1998) concluded that a genetic or biological cause was implicated in the majority of cases of severe ID, while mild ID was more likely to be linked to environmental factors. Environmental factors associated with ID include prematurity, infections (meningitis and encephalitis), traumatic brain injury chemical exposures (radiation) and threats to development such as lack of stimulation (Gillberg and Soderstrom 2003).

## **2.2 Genetics of Intellectual Disability**

In recent years, advances in molecular biology have enhanced our knowledge of genetic conditions associated with ID. This advance in understanding has transformed the study of ID and allowed early diagnosis and the identification of the biological, physical, cognitive and behavioural phenotype characteristics of genetic syndromes.

There are now over one thousand known genetic syndromes associated with ID, most of which are associated with severe ID (Oliver and Hagerman 2007). Individual genetic syndromes are rare. However, the estimated overall prevalence of this group of conditions collectively is thought to be 0.5% of the total population and to constitute a substantial proportion of the ID population (Gillberg and Soderstrom 2003). The most common cause of ID associated with a genetic condition is Down syndrome (1:800/1,000) followed by Fragile X syndrome (1:3,600). Other genetic conditions associated with ID are Angelman syndrome (1:30,000), Cri-du Chat syndrome (1:50,000), Smith-Magenis syndrome (1:25,000), Prader-Willi syndrome (1:20,000), Rett syndrome (1:12,000 girls), Cornelia de Lange syndrome (1:40,000) and Williams syndrome (1: 20,000/30,000).

Genetic syndromes are caused by abnormalities in the expression of genes resulting from alterations in the number, structure or expression of genes or chromosomal regions. Numerical irregularities are associated with the loss of one of a pair of chromosomes or with the formation of an extra copy of the chromosome. Examples of numerical chromosomal anomalies are Trisomy 21 or Down syndrome, 47,XYY syndrome, and Klinefelter syndrome (XXY syndrome). Structural chromosomal anomalies are associated with a deletion (the loss) of a part of a chromosome, or duplication or insertion of additional material. Examples of structural anomalies include the 4p- and 5p- syndromes, 22q11.2 deletion syndrome (also known as Velocardiofacial syndrome, Shprintzen syndrome or di George syndrome), Williams syndrome, some cases of Smith-Magenis syndrome, Prader-Willi syndrome and Angelman syndrome. Genetic syndromes associated with a single gene mutation are numerous, including Fragile X syndrome, Rett syndrome and Tuberous sclerosis (see Table 2.2).

**Table 2.2 Genetic syndromes associated with ID**

<b>Syndrome</b>	<b>Incidence</b>	<b>Genetic cause</b>	<b>ID</b>
Down	1:800/1000	Trisomy 21	Mild to Moderate
Fragile X	1:3,600	Mutation affecting expression of the FMR1 gene at Xq27.3	Mild to Moderate
Prader-Willi	1: 20,000	Paternal deletion or maternal uniparental dysomy (UPD) at 15q11-13	Borderline to moderate
22q11 deletion	1:4,000	Deletion on chromosome 22 (usually)	Mild to moderate
Williams	1:20,000/30,000	Micro deletion on chromosome 7	Moderate to mild ID.
Rett	1:10,000/15,000	Mutation in <i>MECP2</i>	Severe to profound
Angelman	1:30,000	Multiple mechanisms affecting UBE3A located at 15q11-13	Severe to profound
Smith-Magenis	1:25,000	Mutations affecting the retinoic acid-induced gene 1, RAI1, at 17p11.2	Moderate
5p-	1:50,000	Partial deletion 5p	Severe
Cornelia de Lange	1:40,000	Mutation in 3 genes: NIPBL, SMC <sub>1</sub> A and SMC <sub>3</sub>	Severe/profound
1q36	1:5,000/10,000	Deletion on short arm of chromosome 1	Moderate to severe
Rubinstein-Taybi	1:125,000	Microdeletion at 16q13.3 or mutation in the CREB-binding protein gene	Moderate to severe
Lesch Nyhan	1:380,000	Deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT). The mutation is the HPRT1 gene located in the long arm of the X Chromosome.	Moderate

Differences in genomic imprinting and in the structure and the number of chromosome regions lead to different genetic syndromes, with potentially characteristic physical, social, cognitive, behavioural and emotional phenotypes. One of the greatest challenges in the study of such phenotypes is the understanding of the similarities between individuals with the same disorder given that there may also be individual differences amongst those with the same disorder and similarities between individuals with different aetiologies.

The chromosomal anomalies associated with Prader-Willi syndrome and Angelman syndrome are located at 15q11.13. The differences between the two syndromes can be described at a genetic level: the latter is associated with the lack of expression of maternally-transmitted information and the former with the lack of expression of paternally-derived information on chromosome 15 (Dykens and Hodapp 2001). Clinically, Prader-Willi syndrome is characterised by hypotonia, short stature, hypogonadism, feeding problems during infancy and then obesity. The phenotype of Angelman syndrome is characterised by severe developmental delay, severe speech impairment, gait ataxia and also often seizures. Differences in behaviour are also manifest. The behavioural phenotype of PWS includes hyperphagia, temper outbursts, self-injury, repetitive speech, impulsiveness and sleep difficulties (Boer and Clarke 1999). The behavioural phenotype of AS includes an inappropriately happy demeanour characterized by frequent laughing, smiling, excitability and fascination with water (Horsley and Oliver 2006a). Hence, differences in the expression of genetic information can result in different syndromes with differing typical characteristics even though the genes involved are closely associated.

The above example illustrates how aetiology-specific studies have led to greater understanding of specific conditions affecting individuals with ID. Moreover, these studies have identified individual variability within the same syndrome. Subtle differences in the genetic mechanisms underlying the same condition lead to variability in the severity of the phenotype: in behavioural manifestations and level of ID. Behavioural and physical variations are reported in cases of Prader-Willi syndrome with paternal deletion and maternal uniparental disomy (UPD) as well as in cases with Angelman syndrome, where those with paternal UPD present with milder phenotypes than do cases with maternal deletions. Better growth, milder seizures and a greater

ability to use communication such as signing and gesture are reported in cases with paternal UPD (Dykens and Hodapp 2001).

Interest in aetiology-based research has increased in the last 10-20 years, in particular amongst researchers exploring the behavioural characteristics of individuals with genetic syndromes (Hodapp 2004a). The extent to which different aetiologies of ID lead to characteristic differences in physical, cognitive, social, behavioural and emotional phenotypes is a focus of investigation. There is great variation in the behaviour of individuals within genetic syndromes, which highlights the fact that factors other than genetics are associated with each syndrome. The interest in understanding genetic syndromes has increased not just in the genetic field, but also in psychology and neuroscience, leading to collaboration amongst professionals of different fields. These interdisciplinary studies have led to the recognition of a link between gene, behaviour and environment in shaping the phenotype of those affected by a genetic disorder.

The rest of this chapter will explore the concept of behavioural phenotype, how the study of behavioural features has increased our knowledge of the relationship between genotype and phenotype and how comparison studies between syndrome groups and within individual syndromes are now providing more evidence of the interrelationship between gene, behaviour and environment.

### **2.3 Behavioural phenotypes**

The term phenotype refers to an observable trait or characteristic determined by differences in DNA in individuals. The influence of genetic inheritance may be considered straightforward in relation to certain traits such as height or colour of hair

but establishing the degree of influence over other potential features of a phenotype, such as cognitive style or behaviour, is more complex as these may also be shaped by environmental factors during development. The essential question often raised in genetic and behavioural studies is the extent to which it is our genetics or experience that contributes to our resulting behaviour. This debate is explored in different areas, and many disciplines have contributed to our understanding of this complicated topic. One of the areas of research that has contributed to the understanding of the relationship between genes, behaviour and environment is the study of behavioural phenotypes in rare genetic syndromes. The extent to which behaviour is characteristic across different individuals who share the same genetic condition and different from that among other people with alternative conditions that give rise to a similar general developmental disadvantage (e.g., level of ID) provides evidence of a genetic as opposed to developmental origin. So, while it is now well accepted that genotype and environment interact to shape the phenotype, the study of genetic syndromes allows us to understand how mutation in genes leads to differences between conditions and how environmental factors determine variability within a diagnostic category (O'Brien 2000).

Historically, the concept of a behavioural phenotype originates from psychological research into the behavioural patterns of animals in a laboratory setting (O'Brien 2000). The first to refer to the behavioural feature of different genetic conditions employing the term behavioural phenotype was Nyhan, who adopted the terminology to describe the characteristic self-injurious behaviour of children with Cornelia de Lange and Lesch-Nyhan syndromes (Nyhan 1972). However, Nyhan's focus was on a single behaviour, self-injury.

With advances in understanding mechanisms underlying genetics and neuropsychology, the term, behavioural phenotype, has broadened. O'Brien and Yule

(2002, p.2) define a behavioural phenotype as a “ ...characteristic pattern of motor, cognitive, linguistic and social observations that is consistently associated with a biological disorder”. Although this definition emphasises the fact that patterns of behaviour are syndrome characteristics, O’Brien and Yule (2002) also emphasise that patterns of behaviour need not be universal. Other variables are involved: environmental, biological and developmental variables interact continually to shape the phenotype. For example, interactions between the person and his or her social environment are important experiences that can influence the person’s behavioural development. Hence, a complete understanding needs to include how these interactions strengthen and/or weaken the person’s behaviour (Hodapp 2004a). As a result, one needs to introduce the notion of probability and depart from mechanistic determinism to formulate how a variety of factors, including genes, can influence a behavioural phenotype (Hodapp 2004b; Dykens and Hodapp 2007).

Hodapp (1997) described three possible relationships between a genetic syndrome and a behavioural phenotype: no-specificity, whereby it is believed that there are no syndrome-specific links and no characteristic differences in behaviour between individuals with different genetic conditions; total-specificity, whereby it is believed that a characteristic pattern of behaviour is unique to the genetic syndrome and is not found in other conditions; partial-specificity, whereby it is believed that there is a greater likelihood that a characteristic pattern of behaviour will be seen in a particular genetic syndrome than in other conditions, although such behaviour may not be unique to the syndrome. Consistent with this third view, Dykens (1995, p. 523) defines a behavioural phenotype as “...the heightened probability or likelihood that people with a given syndrome will exhibit certain behavioural and developmental sequelae relative to those without the syndrome”.

Although the concept of total specificity can be applied for example to describe the hyperphagia in PWS and the smiling and laughing in AS (these behaviours have not been described in any other syndrome so far) (Oliver et al. 2010), the concept of partial specificity has been demonstrated by several studies. Self-injurious behaviour (SIB) is commonly reported in Cornelia de Lange, Cri du Chat, Smith-Magenis, Lowe, Fragile X, and Prader-Willi syndromes (Arron et al. 2011). Hyperactivity is found more often in children with 5p- deletion and Fragile X syndromes, while repetitive behaviour is more common in Fragile X, Cornelia de Lange, Prader-Willi, Cri du Chat, Smith-Magenis and Lowe syndromes (Moss et al. 2009). However, these studies have also emphasised that there is not only variability between groups of syndromes but between individuals within the same syndrome. Moreover, although SIB is a behaviour shown by individuals with different genetic conditions, comparison studies have shown that a specific topography of the behaviour is associated with a specific syndrome (Oliver et al. 2010): Prader-Willi syndrome is associated with scratching, Cri-du Chat syndrome with self-pulling and rubbing and Cornelia de Lange syndrome with self-hitting and pulling (Arron et al. 2011).

Table 2.3 summarises behavioural features found to be associated with each syndrome groups.

**Table 2.3 Behavioural profiles associated with genetic syndromes**

<b>Syndrome</b>	<b>Behavioural features</b>
Down	Varies with age. Anxiety associated with sensory sensitivity, hyperactivity and impulsivity and autistic features. High risk of early onset of dementia.
Fragile X	Social anxiety, hand flapping and stereotypic behaviour, hyperactivity and self-injury.
Prader-Willi	Hyperphagia, outbursts, mood abnormalities, skin picking, repetitive speech and questioning, OCD.
22q11 deletion	Poor social interaction skill, avoidance of eye contact, excessive response to threatening stimuli, fearfulness of painful situation. Attention difficulties and high level of anxiety and depression. High rate of bipolar, attention deficit disorder and psychosis.
Williams	High level of language abilities. Social disinhibition and inappropriate friendliness, generalised anxiety attention problems and hyperacusis.
Rett	Hand stereotypies, breathing abnormalities, sleep disturbances, anxiety and fear.
Angelman	Inappropriate laughing and smiling. Very sociable, fascination for water, hyperactivity and sleep disturbances in childhood.
Smith-Magenis	Friendly and eager to please. Enjoy adult interaction. High level of impulsivity, hyperactivity, irritability, distractibility. Aggression, temper tantrum and self-injury. Self-hugging and putting objects into orifices.
5p-	Cat-cry during infancy. Hyperactivity, poor concentration/distractibility, impulsivity, aggression, temper outbursts, self-stimulatory/repetitive behaviour, and self-injury behaviours.
Cornelia de Lange	Great variability in behaviour, however most common features reported are: over-activity, irritability, distractibility, autistic features and self-injury.
1q36	Self-injury, temper tantrum, aggression, throwing or banging objects, striking people, screaming and autistic features.
Rubinstein-Taybi	Friendly and happy disposition, resistance to change, self-stimulatory behaviour such as rocking spinning and hand flapping.
Lesch-Nyhan	Severe self-injurious behaviours, such as lips and fingers biting and aggressive behaviours. These manifestations are generally involuntary.

Variability in the phenotype within individuals with the same syndromes raises questions relating to the complex relationship between genes, behaviour and environment. Such variability may be explained in terms of genotypic expression, such as the location of the mutation or the parent of origin of the mutation. Such factors could influence the severity and/or the presence of a specific difference in the phenotype. In Prader-Willi syndrome, for example, a distinction exists between the

individual who has a deletion in the chromosome from the father (paternal deletion) and individual who has two chromosome 15s from the mother (maternal uniparental disomy, UPD). Those with UPD have a higher rate of psychosis than those with paternal deletion. They also differ in terms of cognitive profile. For example, individuals with paternal deletion show higher levels of skill in tasks such as putting together a jigsaw (Dykens 2002), while those with a deletion were associated with a significant lower IQ score (Roof et al. 2000). The role of environmental factors in influencing the behaviour needs to be analysed when exploring variability within syndrome. For example, Rett syndrome mouse model studies have demonstrated that an enriched environment (with sensory, motor and cognitive stimulation) improved symptoms in the mutant mice (Kondo et al. 2008). Thus individualised intervention and environmental stimulation are factors to be taken into consideration when investigating and planning intervention.

Evidence shows that the reactions of parents to the individual can have reinforcing properties influencing expression of the behaviour. For example, it has been shown that the inappropriate laughing and smiling of children with Angelman syndrome is positively reinforced by the social environment (Oliver et al. 2002). Hence it is essential to consider factors that influence the developmental course of the syndrome and individual-environmental interaction over time (Hodapp 2004a).

As understanding and knowledge grows about the differences and similarities between syndromes, the study of variability within syndromes is now increasing. Analysis focuses on exploring relationships between genotypes and phenotypes. Within syndrome studies aim to understand differences between types of mutation and gender and also to explore how behavioural, cognitive, social and emotional features change over time, throughout infancy, childhood, adolescence and adulthood. Several studies

have suggested biological and environmental influences may change over time and hence longitudinal studies are important.

In summary, the study of behavioural phenotypes aims to find links between genetic variation and behaviour. One way to achieve this is to study different syndromes and the differences and similarities between and within syndromes. There are potential benefits of such studies in terms of diagnosis, early intervention and guidance for those involved in supporting the individuals concerned (i.e., families, professionals, carers and advisory or support groups). The understanding of the developmental course of a syndrome can lead to the identification of early signs of the disorder which prompt medical and genetic testing. Earlier diagnosis can lead to earlier intervention. For example, PKU is a genetic syndrome that can be effectively treated if confirmed early in life. Families can be provided with information about the strengths and weaknesses of the individual and understanding of the syndrome can help parents to overcome feelings of guilt that they might be to blame for their child's problems.

## CHAPTER 3

### RETT SYNDROME: CLINICAL AND GENETIC FEATURES

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#### 3.1 Introduction

Rett Syndrome (RTT) is a neuro developmental disorder first described by Dr. Andreas Rett in 1966, a pediatrician in Vienna, who observed similar behavioural and physical characteristics in two of his patients (Rett 1966 cited in Hagberg 2002). His interest was drawn to those characteristics that now are considered to be the hallmark of Rett Disorder: developmental stagnation and then regression, gait apraxia and hand stereotypies. Dr. Andreas Rett published his findings in German in 1966, however his work would remain unknown to the English-speaking scientific community for another 17 years.

Dr. Bengt Hagberg, a physician (paediatric neurologist) in Sweden, independently recognised the same disorder and between 1960-1980 examined girls with the same developmental disorder and a “curious and unexplained hand wringing” (Hagberg 2002). Following a paper presented at the European Federation of Child Neurology in Manchester in 1980, it appeared that the same syndrome had been described in other countries, but not yet recognized as an entity. In 1983 Hagberg, Aicardi, Dias, and Ramos published a report on 35 girls in Sweden, France and Portugal, who shared the same clinical features as the patients described in the 1960’s by Dr. Andreas Rett in Vienna (Hagberg et al. 1983). This report raised awareness and details of the syndrome became available to a wide community.

The first diagnostic criteria for RTT were developed in 1988 by a group of clinicians to help with the diagnosis of the syndrome (Diagnostic Criteria Working Group 1988).

The criteria were revised in 2002 and again in 2010 following new discoveries in the clinical, genetic and neurobiological features of Rett Syndrome (Hagberg et al. 2002; Neul et al. 2010). Neul et al. (2010) Diagnostic Criteria for Rett Syndrome are shown in table 3.1 – 3.2 (See appendix A for Hagberg et al. (2002) Diagnostic criteria).

**Table 3.1 Revised Diagnostic criteria for Rett Syndrome (Neul et al. 2010)**

<b>Required for Typical RTT</b>	<b>Required for Atypical RTT</b>
1. A period of regression followed by recovery or stabilization	1. A period of regression followed by recovery or stabilization
2. All main criteria and all exclusion criteria	2. At least 2 of the 4 main criteria
3. Supportive criteria are not required, although often present in typical RTT	3. 5 out of 11 supportive criteria

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**Main criteria**

1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of acquired language
3. Gait abnormalities: impaired (dyspraxic) or absent ability
4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms

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**Exclusion criteria for typical RTT**

1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that cause neurological problems
  2. Grossly abnormal psychomotor development in first 6 months of life
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**Supportive Criteria for RTT**

1. Breathing disturbances when awake
  2. Bruxism when awake
  3. Impaired sleep pattern
  4. Abnormal muscle tone
  5. Peripheal vasomotor disturbances
  6. Scoliosis/kyphosis
  7. Growth retardation
  8. Small cold hands and feet
  9. Inappropriate laughing/screaming spells
  10. Diminished response to pain
  11. Intense eye communication –eye pointing
-

**Table 3.2 Revised Diagnostic Criteria for Variant form of RTT (Neul et al. 2010)**

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**Variant form of RTT (meet criteria for atypical RTT)**

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**Preserved Speech Variant (Zappella Variant)**

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*Clinical Features*

- Regression at 1-3 yrs, prolonged plateau phase
- Milder reduction of hand skills
  - Better retained hand use
- Recovery of language after regression
  - Mean age of recovery is 5 yrs
  - Single words or phrases
- Milder Intellectual disability (IQ up to 50)
- Autistic behaviour common
- Decrease frequency of typical RTT features
  - Rare epilepsy
  - Rare autonomic dysfunction
  - Milder scoliosis/kyphosis
  - Normal head circumference
  - Normal height and weight in most

*Molecular genetics*

Mutations in *MECP2* found in the majority of cases

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**Early Seizure Variant (Hanefeld Variant)**

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*Clinical Features*

- Early onset of seizures
  - Before 5 months of life
  - Infantile spasms
  - Refractory myoclonic epilepsy
  - Seizure onset before regression
- Decrease frequency of typical RTT features

*Molecular Genetics*

Mutation in *MECP2* rarely found

Analysis for mutations in *CDKL5* should be performed

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### **Congenital Variant (Rolando Variant)**

#### *Clinical Features*

- Grossly abnormal initial development
  - Severe psychomotor delay
  - Inability to walk
- Severe postnatal microcephaly before 4 months
- Regression in first 5 months
- Lack of typical intense RTT eye gaze
- Typical RTT autonomic abnormalities present
  - Small cold hands and feet
  - Peripheral vasomotor disturbances
  - Breathing abnormalities while awake
- Specific movement abnormalities
  - Tongue stereotypies
  - Jerky movements of the limbs

#### *Molecular Genetics*

Mutation in *MECP2* rarely found

Analysis for mutations in *FOXP1* should be performed

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### **3.2 Clinical features of RTT**

RTT is a rare genetic condition that affects 1 in 12000 females (live birth). In its classical form, RTT is characterized by reduction in brain growth, involuntary movement in particular in the hands, irregular breathing, disturbed muscle tone and postural difficulties, loss of previously acquired skills, such as speech and fine motor skills (Kerr 2003). The brain regions most affected are the hippocampus, cortex and cerebellum, areas concerned with thinking, movement, speech and fine motor skills (Kerr 2003; Weaving et al. 2008).

To support the clinical classification of the syndrome a system of four stages was developed (Hagberg and Witt-Engestrom 1986). The Swedish staging system consist of four clinical stages: Stage I or Early onset Stagnation, Stage II or Developmental Regression, Stage III or Pseudostationary period, Stage IV or Late motor deterioration. More recently, two subgroups to stage IV were introduced, Stage IVA, which includes individuals that were ambulant, but have now lost the mobility and Stage IVB, which includes individuals that never walked (Hagberg 2002). The British Survey classifies the stages of the syndrome as Pre-Regression (Stage 1), Regression (Stage 2) and Post-Regression (Stage 3-4). Table 3.3 summarizes the features of each stage.

**Table 3.3 Swedish and British stage classification (Hagberg and Witt Engestrom 1986; Hagberg 2002; Kerr and Witt Engerstrom 2001)**

<i>Swedish classification</i>	<i>British classification</i>	<i>Features</i>
<i>Stage I (Early Onset Stagnation)</i>	<i>Pre-Regression</i>	<i>Quiet and placid, postural and movement delay. Slow in learning and movements. Onset: from 5 month of age</i>
<i>Stage II (Developmental Regression)</i>	<i>Regression</i>	<i>Reduction of skills such as speech, hands skills, personal contact. Increase in involuntary movement such as hand-mouth movements, bruxism. Screaming, night laughing and sleep disturbances. Breath holding and deep breathing toward the end of the stage. Seizure. Onset: 1-3 years</i>
<i>Stage III (Pseudo-Stationary period)</i>	<i>Post-Regression</i>	<i>“Wake up” period. Common problems are deficiency in growth, abnormal muscle tone, epileptic seizure, irregular breathing, sleep disturbances, problems with feeding and nutrition, a slow onset of spasticity. Onset: after Regression. Can last from years to decade.</i>
<i>Stage IV (Late motor deterioration)</i>		

### 3.2.1 Pre-regression

One of the necessary inclusion criteria for RTT is normal development through the first 6 months of life (Hagberg 2002), however evidence in the literature suggests that the child with RTT displays sign of developmental delay during the first month of life, in particular disturbance of general movements have been highlighted (Burford et al. 2003; Burford 2005; Einspieler et al. 2005; Einspieler et al. 2005b; Huppke et al. 2003;

Leonard and Bower 1998). Although it is still not clear when the disorder has its onset, there is evidence in the clinical literature that suggests the onset of RTT is often before birth (Guy et al. 2001; Kerr 2003; Kerr and Witt Engerstrom 2001; Nomura et al. 1997). Examination of early developmental history highlights that the child, although reaching some of her development milestones, is delayed from birth.

Parents report unusual behaviours in the first 6 months and the child is described often as placid and floppy (Leonard et al. 2005). Kerr et al. (1987) reported early abnormalities of the hands such as excessive patting and waving of the hands and arms, abnormal alternating hand movements and general incoordination seen in all 4 cases by the age of 11 months. Other studies reviewing videos taken before the regression stage have confirmed the presence of stereotypies and unusual movements before the onset of the disorder (Burford et al. 2003; Burford 2005; Einspieler et al. 2005). Temudo et al. (2007) reported a case of a 19 months old girls with RTT with repetitive and dystonic movement (stereotyped manipulation of toys, repetitive dystonic movement of the right limbs and stereotyped facial movement such as closing of the eyes, tongue protrusion and grimacing) before regression. Segawa (2005) reported delay in motor milestone from infancy, such as delays in establishing head control, rolling over and sitting. The delay was especially evident for crawling. Only 10% of the 38 patients were reported to be able to crawl before 10 months. In the other 90%, crawling was delayed or not achieved. In addition, hand motor skills were delayed. Reaching out, pincer grasp and transfer from one hand to the other were the skills most affected. Retrospective analyses of parental report highlighted that the child showed some behavioural problems soon after birth, such as unresponsiveness to environmental stimuli, autistic features and hypotonia. Video analytic studies emphasised the early presence of abnormal movements (Witt-Engestrom 1987). Witt-Engestrom (1992) also reported that the first

signs most often reported by parents and professionals were delay in reaching gross motor skills, the lack of anticipation, vague social contact, irritability and slow responses. Einspieler et al. (2005) analysed videos of normal infants and infants that later developed RTT to study the early movements in infants. The study revealed the presence of jerky uncoordinated movements, poor general movements and none of the girls with RTT had normal fidgety movements. Although the absence of fidgety movement is not predictive of RTT, evidence suggests that the presence of those movements are predictive of normal development (Prechtl et al. 1997). Similarly observations from professionals of home videos revealed perturbation in their development. In particular, both midwives and health professionals made some comments on physical appearance and hand posture in the first months of life (Burford 2005).

Signs of the disorder become increasingly apparent during the first years: development of repetitive movements of the hands and arms becomes increasingly evident, mobility is poor and crawling is rare, and both speech and creative play are quite uncommon (Kerr 2002). It is not unusual for the child to develop milestone skills such as reaching, grasping, feeding, walking and some speech or babble. However those skills are then lost or reduced once the regression stage of the disorder strikes.

### *3.2.2 Regression*

The regression stage often begins suddenly after an apparently normal early development and can last from months to years. Unexplained attacks of screaming, social withdrawal and marked involuntary movements are hallmarks of the stage. During the regression stage, there is a reduction of previously acquired functional skills, the loss of speech, decreased hand use, disturbed muscle tone, sleep dysfunction and

breathing abnormalities. A characteristic feature is the loss of purposeful hand function and the appearance of intense and continuous stereotyped hand movements that include clapping, squeezing and rubbing.

In a study exploring regression in 53 individuals with RTT, Charman et al. (2002) reported a mean age of regression of 16 months and the loss of hand skills and the ability to communicate were the most common abilities lost during regression. Decrease in motor skills were reported in almost half of the sample (49.1%), however regression in motor skills was a feature reported in older patients reflecting the issue that the loss of motor abilities may be part of the deterioration of muscle tone, joint contracture and scoliosis (Charman et al. 2002) rather than features of the regression. Evidence in the literature suggests that the age of regression can be considered an index of severity (Charman et al. 2002). Early regression results in severe cases, late regression results in milder cases. Huppke et al. (2003) suggested that children with an early regression are less likely to walk and that there appears to be a period when the girls can learn functional skills.

Loss of hand use and language, abnormalities of gait and the development of hand stereotypies are the areas of development most affected in the Rett phenotype during the regression stage. Delay in the ability to speak, sit, crawl and walk (Nomura and Segawa 2005) is common together with the loss of feeding abilities (Larsson et al. 2005). Behavioural manifestations are also common during this stage, with inappropriate laughing and screaming, autistic features and autonomic disturbances while awake, such as breath holding and deep breathing (Kerr and Witt Engerstrom 2001). Witt Engerstrom, using data from the Swedish cases of girls and women with RTT (1992), reported the loss of skills in areas such as hand use and functional hand skills, communication and social interaction, and babble and words.

Towards the end of the regression stage, hand stereotypies, teeth grinding, breathing abnormalities, spells of screaming and laughter begin to appear.

### *3.2.3 Post-regression*

After the regression stage the child tends to stabilize, and often recovers some of the skills lost during regression, although the consequences of the disorder results in severe physical and intellectual disability. The effect of the disorder is clearly displayed in growth, muscle tone, mobility, voluntary movements, feeding problems due to problems in swallowing and chewing difficulties and scoliosis is present in about 60% of subjects (Kerr 2003). Epilepsy, which usually appears after regression, occurs in 80% of females affected by RTT (Jian et al. 2007). Autistic features often disappear and social interaction tends to improve, however manifestations of abnormal autonomic activity, such as breathing abnormalities, begin to appear. In young girls EEG may appear abnormal, suggesting epilepsy, but not connected with clinical epileptic seizures (Kerr 2003). Behavioural manifestations associated with RTT such as breathing irregularities, breath holding, hyperventilation and episodes of motor activities (i.e. twitching, jerking movements) are often confused with epileptic seizure (Weaving et al. 2008).

### ***3.3 Clinical variability of RTT***

Since its first description, different variants of RTT have been described in the literature, with a characteristic pattern of age of onset, clinical profiles, seizures and communication abilities (see table 3.2 for Diagnostic criteria for variant form of RTT).

Below is a short description of some of the variants or atypical forms of Rett Syndrome.

### *3.3.1 Congenital variant*

First described by Rolando in 1985, girls with the congenital variant of RTT are reported to be placid, floppy and showing some signs of delayed development from the first months of life. Mutation in FOXP1, located in the chromosome band 14q12 and encoding a brain-specific protein required for early development of the CNS, was found to be associated with the congenital variant (Ariani et al. 2008). Van der AA (2011) reported two cases (1 male and 1 female) with novel FOXP1 mutation. Clinical features reported were the regression of previously acquired skills, hypotonia, abnormal development, delay in eye contact, regression in the first few weeks affecting head control, hand use, crying and feeding difficulties. Seizures were reported in one of the patients starting at 4 months of age with infantile spasms. Lack of speech, hand stereotypies, inappropriate laughing and teeth grinding were also reported.

### *3.3.2 Early onset seizure variant*

The early onset of seizures variant, also known as the Hanefeld variant, may be caused by mutation in the cyclin-dependent kinase-like 5 gene (*CDKL5*). *CDKL5* is located on the X Chromosome and mutations have been identified in both females and males. Reports from the literature consistently identify the early onset of seizures as the main clinical feature of the disorder. Cases with this variant form of RTT are reported to be placid and sleepy as babies with the onset of seizures at or before 3 months of age. Other features are: hand stereotypies, lack of eye contact, scoliosis, absence of speech, small and cold feet. There is also delay in social interaction and autistic features have been reported (Bahi-Buisson et al. 2008; Evans et al. 2005).

### 3.2.3 Preserved speech variant

The preserved speech variant, also called the Zapella variant, includes mildly affected cases in whom some speech and motor skills are preserved. Ranieri et al. (2009) described 29 cases with the variant all with *MECP2* mutation. The girls presented with better language and hand use, late regression and autistic features.

### 3.2.4 Male variant

Male cases with RTT have been diagnosed based on clinical criteria. Coleman et al. (1990) and Philippart (1990) first described males with some RTT features. Masuyama et al. (2005) reported a case of a male with classic RTT with R133C mutation. The sister and the mother of the affected boy were shown to carry the same mutation. The mother had a mild ID and the sister was also diagnosed with classic RTT. The boy's development was delayed at 3 months of age, with hand stereotypies noted at 5 years of age, by which time he was not able to walk, although he could stand with support by 6 years of age and presented with breathing abnormalities during waking periods. Budden et al. (2005) also described a male with RTT in a familial recurrence of the syndrome. His mother was a carrier of RTT with skewed inactivation of the X- chromosome; his older sister was diagnosed with atypical RTT. Clinical features included the impairment of motor abilities, regression of language and development of hand stereotypies, breathing abnormalities, seizures and scoliosis.

## 3.4 Genetic basis of RTT

A major discovery occurred in 1999, when the gene involved in causing RTT was identified (Amir et al. 1999). RTT was found usually to be associated with mutation in the methyl-CpG binding protein-2 (*MeCP2*) gene, located on the X chromosome at

Xq28. Almost all mutations are sporadic and occur *de novo* and the majority are of paternal origin. However familial cases have been described in the literature (Kerr and Ravine 2003; Kerr and Witt Engerstrom 2001). Familial recurrences include about 1% of the total reported cases (Schanen et al. 1997). To date about 10 cases of familial cases have been described in the literature. As RTT is usually sporadic, the linkage to a genetic inheritance model was difficult. Initially various models were proposed and after the identification of a family with two half sisters affected and a family with a maternal aunt and niece with RTT, the proposed hypothesis was of a X linked disorder, lethal in male caused by a mutation in the X chromosome (Van den Veyver and Zoghbi 2002).

In 1998 the identification of a Brazilian family with three sisters with RTT allowed the localization of the gene to Xq28 (Siriani et al. 1998; Webb et al. 1998; Webb and Latif 2001). Screening of genes in chromosome band Xq28 allowed mutations in the *MECP2* gene to be found.

Although *MECP2* mutation is found in at least 95% of Classic cases of RTT it is important to emphasize that RTT remains a clinical rather than a molecular diagnosis. *MECP2* mutations are not found in all RTT cases and the mutation has been found in individuals who do not meet the clinical diagnostic criteria for classic or variant RTT (Hagberg 2002). Mutation in the *MECP2* gene has been reported to be associated with a wide range of different clinical disorders in both females and males. In females, the phenotypic spectrum varies from the classical Rett Disorder, ID and seizure, Autism, Mild ID to normal carriers. Several male cases with Rett phenotypes have been described in the literature (Budden et al. 2005; Coleman 1990; Philippart 1990; Topcu et al. 2002). In males, as the mutations that cause RTT in females usually result in a much more severe encephalopathy from the newborn period, the mutation will take

effect in every cell. Only if the boy is functionally mosaic, either if he has Klinefelter syndrome or if he shows somatic mosaicism for the mutation, is he likely to show a classic RTT phenotype. Other mutations that are less likely to manifest in females may cause non-progressive and either syndromic or non-syndromic ID. The phenotype associated with *MECP2* mutation in males include progressive encephalopathy (Schanen et al. 1998), a classical Rett like phenotype (Clayton-Smith et al. 2000), sometimes associated with Klinefelter syndrome (Schwartaman et al. 1999; Vorsanova et al. 1996) or somatic mosaicism/developmental delay (Schanen 1998); and X-linked ID with progressive spasticity (Meloni et al. 2000). Hence the phenotype of males varies mostly due to the type of mutation. If the boy carries a mutation that inactivates the protein, the child dies in the first year due to the severity of the phenotype, if the boy has a mutation that truncates the protein but keeps the two key domains intact, the male will have ID/seizure/balance problems and tremors (X-linked ID).

Severity of the RTT phenotype is determined in part by the type of mutation (see section 3.4 for genotype-phenotype association studies) and in part on the pattern of X chromosome inactivation. Huppke et al. (2006) examined the clinical and genetic phenotype of three patients with a very mild phenotype with mutation in the *MECP2* gene. The patients did not fulfil the clinical criteria for RTT but were found to have mutations (Late deletion and Missense mutation) that are common in the Classic form of the disorder. X inactivation analysis showed that all three patients had skewed X inactivation. As RTT is an X linked disorder and *MECP2* is subject to X inactivation this could explain the differences in severity between the same groups of mutation. Archer et al. (2007) examined the relationship between clinical severity and X-Inactivation of girls with the R168X and T158M mutation and found that cases with greater severity was associated with a higher proportion of active copy of X

inactivation. These studies may indicate that X-inactivation may explain some differences in the severity of the phenotype in girls with the same mutation.

#### 3.4.1 *The MeCP2 protein*

MeCP2 was first identified by Lewis et al. (1992) who isolated the protein from a rat brain and Naan et al. (1993) showed and defined the methyl-CpG binding domain (MBD). MeCP2 is a nuclear protein that binds methylated DNA. This is thought to regulate transcriptional repression and is a member of the group of methyl-CpG binding proteins. It is divided into four principal, functional domains: MBD, a transcriptional repressor domain (TRD) and N- and C- terminal domains. Yet, the function of the N- and C- terminal domains is still not well understood, though it appears that the protein helps the expression of gene activity by regulating RNA splicing, and chromatin and nucleosome clustering (Archer 2007; Hite et al. 2009; Tao et al. 2009). Chahrour et al. (2008) suggested that MeCP2 could function as both an activator and a repressor of transcription. The authors observed that in the brain of *Mecp2-null* mice, MeCP2 regulates the expression of different genes in the hypothalamus and confirmed that MeCP2 binds to their promoter. Hence, this hypothesis suggests that MeCP2 may act as transcriptional mediator rather than transcriptional repressor.

MeCP2 regulates gene activity primarily in the maturation of neurons. This function of the MeCP2 is consistent with some of the features found in RTT, e.g., apparent normal development and reduced brain size (Singh et al. 2008).

### 3.5 Phenotype-genotype association in Rett Syndrome

Since the recognition that mutation in the *MECP2* gene causes RTT, research has been investigating the role of the gene and its association with the symptoms and severity of the condition.

Significant progress has been made in genetic studies of RTT with the description of the genes involved in the cause of the disorder; now the interest of the scientific community is turning to investigate the association between genotype and phenotype.

Investigations of *MECP2* in RTT have identified more than 200 different disease-causing mutations, with the nine most common mutations accounting for 78% of the Rett population (Christodoulou et al. 2003).

Studies on the association between genotype and phenotype have led to different results, however evidence of the correlation between genotype and phenotype are now emerging and there is general agreement that the severity of the syndrome can be predicted by the type and location of the mutation (Christodoulou et al. 2003).

An analysis of the nine most common mutations in the *MECP2* gene, has revealed that p.R133C is the mutation associated with the milder phenotypes. Cases with p.R133C mutation reported a delayed onset of regression, delayed onset of hand stereotypies, preserved hand function in two-thirds of individuals and feeding difficulties occurring less commonly. The study also reported that all cases with the p.R133C mutation learned to walk and most of the cases have some language skills (Bebbington et al. 2008). p.R294X was found to be associated with behaviours relating to mood difficulties, body rocking and night time behaviour, p.R133C and p.R306C were found to be associated with higher anxiety and fear. All three mutations have been found to have a milder phenotype by several other studies thus the results from this study could indicate that those individuals may be more able to exhibit those behaviours

(Robertson et al. 2006). Incongruities in the results were reported for those mutations associated with the most severe phenotype. p.R255X and p.R270X were associated with the most severe phenotypes in the Pinada scale and p.T158X in the Kerr scale (Bebbington et al. 2008). Recently, Neul et al. (2008) found that individuals with p.R168X showed the most severe effects of RTT, compared to those with a p.R294X or p.R133C mutation. They are more likely to lose the ability to walk, hand skills and to develop few skills in relation to speech, compared to those with other truncating mutation or a C-Terminal case, who are more likely to retain the ability to walk and speech.

### **3.6 Conclusion**

Mutations in *MECP2* gene are linked to several neurological disorders such as RTT, Angelman syndrome, unspecified severe ID, Autism and neonatal encephalopathy. Duplication of *MECP2* gene is also associated with severe ID, hypotonia, respiratory infection, lack of speech, seizure and spasticity in males.

In the last 10-20 years the understanding of RTT and *MECP2* disorder have increased enormously since the discovery of the gene responsible for it. The scientific community has developed an interest in new, rational therapies. Several strains of *Mecp2* knockout mice have been developed and several attempts have been made to reverse the symptoms after onset. Recently Guy et al. (2007) created a mouse model of RTT in which the endogenous *Mecp2* gene was silenced by inserting a lox-STOP cassette that could be reactivated. The authors were trying to establish whether the symptoms were potentially reversible. The results of the experiment were unexpected. In the heterozygous female mice, RTT-like phenotypic symptoms were improved. The effects of neurological brain damage were thought to be irreversible, however recent

studies have demonstrated that loss of MeCP2 is reversible and the neurons can regain their functionality if MeCP2 is restored in the appropriate time and dosage.

These results bring hope for future treatment for humans, though the possibility of reversal of RTT symptoms in humans is still remote. Providing the correct dosage of MeCP2 to those neurons that lack it remains a challenge as an excessive dose of MeCP2 could cause further damage such as motor dysfunctions (Gadalla et al. 2011). In parallel with the molecular research, therefore, it is important to pursue other strategies that may ameliorate the condition. Environmental strategies are well documented to be beneficial and improve the quality of life in other disorders yet the literature on environmental intervention in individuals with RTT is still limited.

Earlier studies exploring Self-injurious behaviours (SIB) and hand stereotypies highlighted the importance of considering the environment in shaping the behaviour of girls with RTT (Iwata et al. 1986; Oliver et al. 1993) Operant conditioning strategies may be useful and were successful in decreasing the SIB in two girls and a structured learning environment increased compliance and play with toys in one of the girls. Piazza et al. (1993) observed an increase in self-feeding in five girls with RTT using prompting and reinforcement procedure. Moreover, animal studies have demonstrated that an enriched environment (with sensory, motor and cognitive stimulation) improved RTT symptoms (Kondo et al. 2008). Hence the exploration of alternative intervention strategies is timely and appropriate.

**CHAPTER 4**

**THE BEHAVIOURAL PHENOTYPE OF RETT SYNDROME: A SYSTEMATIC  
REVIEW OF THE LITERATURE**

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#### **4.1 Introduction**

Motor and cognitive aspects are primary features for a diagnosis of RTT, however behavioural features have been described to be prominent in the phenotype of the disorder (Coleman et al. 1988, Mount et al. 2002b, Samson et al. 1993) and there has been an increased interest in the behavioural, emotional and cognitive features of RTT since 2000. In particular, hand stereotypies, breathing abnormalities, autistic features and communication abilities have been the focus of research. The most evident characteristics of the behavioural phenotype associated with RTT are the development of repetitive hand stereotypies, such as wringing, clapping or washing hands, loss of functional hand use and a regression in communication and motor abilities (Hagberg et al. 2002). Additional features of RTT are social withdrawal, autistic features, dyspraxia, bruxism, epileptic seizures, scoliosis, breathing abnormalities during wakefulness, feeding and nutritional difficulties and sleep disturbances (Kerr and Witt Engerstrom 2001). In an initial review, Mount and colleagues (2001) found that hand stereotypies were reported in all 38 of the case studies she and her colleagues analysed. Other behaviours were also reported: hyperventilation (84%), indifference to people and/or objects (50%), putting hands in mouth (47%), poor eye contact (39%), holding of breath (37%), grinding teeth (37%), expressionless face (29%), holding hands at the level of the mouth (24%), inappropriate laughing (21%) and sleep abnormalities (21%). Their findings were broadly consistent with the surveys conducted by Coleman and

colleagues (1988) and Samson and colleagues (1993), who also described the presence of self-injury, screaming and fear/anxiety in unfamiliar situations.

Research on the cognitive phenotype has been growing with, in particular, studies exploring the communication and attention abilities of girls with RTT. These studies have highlighted impairment in the ability to sustain attention towards objects and social stimuli, lack of the ability to attend selectively to a specific stimulus and the fact that communication abilities are at the pre-intentional level (Budford and Trevarthen 1996; Fabio et al. 2009a, 2009b; Olsson 1987; Witt Engerstom 1990; Woodyatt and Ozanne 1992, 1994). Sigafos et al. (2009) conducted a review of nine studies published between 1995 and 2005 on the effects of communication intervention in RTT. Generally the aims of the studies were to increase communication abilities by teaching alternative ways of communication. However, they concluded that the literature was limited and characterized by methodological limitations concerning sample size, study design and inclusion of participants. The limited literature on the topic did not allow conclusion of which intervention approach is the best in this population. The certainty of evidence about the intervention was deemed to be adequate for only one study (Van Acker and Grant 1995). This study suggested that a computer based aid for requesting could be beneficial. In fact an increase in requesting was observed in two of the three girls. It is clear that more research is needed to understand the functions and best intervention procedures to increase communication skills in individuals with RTT.

The recognition that RTT is often caused by mutations in *MECP2* (Amir et al. 1999) and the development of a mouse model for RTT (Guy et al. 2001) have led to an understanding that the condition may be characterized by a broad phenotypic spectrum. Since the discovery of the *MECP2* mutation, over 200 mutations have been described in the literature and researchers have now turned their attention to explore the association

between the specific genotype and phenotypic expression. In particular, research has focused on describing the effect a specific mutation may have on the severity of the phenotype. Although conclusions have not been entirely consistent between studies, there is a general agreement that some mutations are associated with milder phenotypes and others with more severe phenotypes. For example, R133C, R306C, R294X and C-Terminal mutations appear associated with lower severity scores and R270X and R255C mutations with higher severity scores (Bebbington et al. 2008; Charman et al. 2005; Neul et al. 2008).

The aim here was to review the literature on the behavioural and cognitive phenotype of RTT from 1983 (first published paper in English) to the present to summarise understanding of the behavioural profile of the syndrome and to identify specific areas that need future research.

#### **4.2 Aims of the review**

The review conducted in 2001 by Mount and colleagues found strong evidence that hand stereotypies and breathing abnormalities are quite consistently found in individuals with RTT but it is yet to be established whether other behavioural features are characteristic of RTT or a general problem of severe ID. The aim was to identify and summarise the literature on the behavioural characteristics of RTT. A systematic search was used to search for literature on the behavioural phenotype of RTT.

The review is divided into four parts to address four questions:

1. What are the behavioural characteristics of RTT described in the literature?
2. Which features are specific to RTT compared to a control group?

3. Are there specific behavioural features of RTT that relate to different mutations in the *MECP2* gene? Does the RTT behavioural phenotype express itself differently across different mutations in the *MECP2* gene?

4. Does the phenotype change across age groups?

In the first part, behavioural characteristics of RTT will be described. The aim is to identify those behaviours potentially characteristic of the phenotype. The second part aims to hone the specification of the phenotype by exploring studies which used a control group to understand common and unique features of the condition. The third part will focus on describing those studies that have investigated the relationship between genotype and phenotype. In the final part, evidence on variation in the expression of the phenotype across age groups will be summarised to analyse whether the behavioural repertoire of RTT changes over time.

### **4.3 Method**

Studies were identified using: an electronic database search, follow up of the reference lists of identified articles and an electronic search of selected journals.

#### *4.3.1 Inclusion and exclusion criteria*

Studies included in the review met the following criteria. They:

1. reported an empirical study,
2. were written in English,
3. were published in a peer-reviewed journal,
4. were published between 1983 and 2011, and,
5. explored either (a) behavioural characteristics of RTT, or (b) the association

between specific genetic mutations (genotype) and specific behavioural features

(behavioural phenotype), or (c) the neurology of characteristic behaviour such as sleep and breathing abnormalities.

Clinical case reports, non empirical studies, studies that focused exclusively on the genetic aspects of the syndrome, studies of animal models of the disorder, and studies that evaluated the effects of clinical, behavioural and communication interventions were excluded from the review (see Sigafos et al. 2009 for a recent review of the latter). Single and multiple case experimental design studies were also excluded from the review.

#### *4.3.2 Search methodology*

Articles included in the review were initially identified through searching 3 databases: PubMed, Web of Science and PsycInfo (1806-2011) using the key term *Rett Syndrome*. Articles with the word Rett Syndrome (or Rett Disorder) in the title or abstract were initially selected for review. The abstract was analysed to check if the study met the inclusion criteria, and, after removing duplicates, a total of 103 studies were identified for review.

A further three studies were identified by examining the reference sections of included studies. A number of journals were also electronically searched to locate potential studies that were not already identified. These were the: Journal of Intellectual Disability Research, Journal of Autism and Developmental Disorder, Brain and Development, Research in Developmental Disabilities, Research in Autism Spectrum Disorder, Journal of Medical Genetics and Disability and Rehabilitation.

No additional studies were identified. However, two extra studies were identified by a later search of Pubmed (November 2010) and one further article was identified on its publication in the Journal of Intellectual Disability Research in 2011. Follow up of

citation and searches of reference lists were carried out until no new papers were identified.

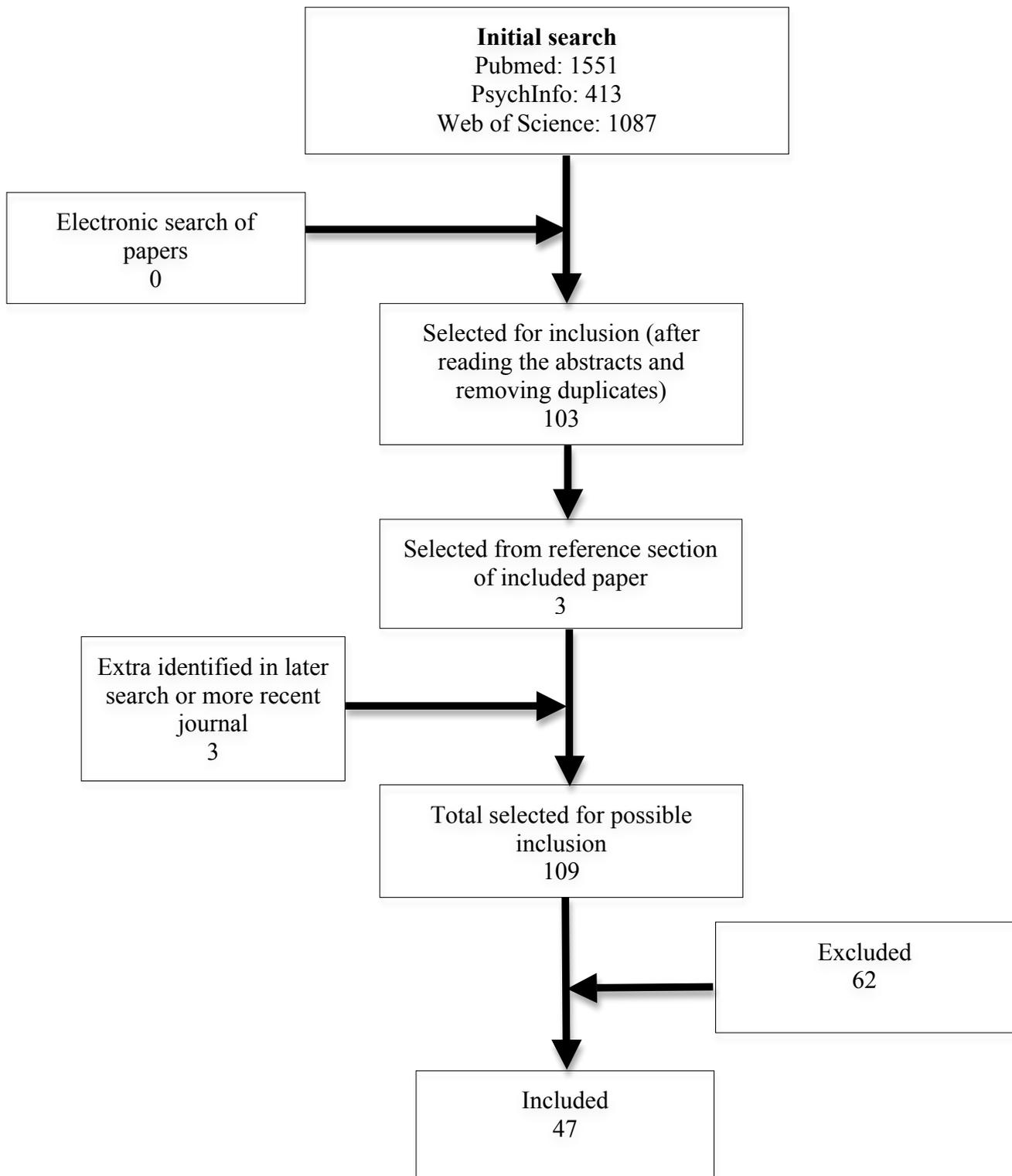
The 109 references found during the database search were stored in reference management software (End Note Web 2.8).

47 studies were included in the review. The other 62 studies were excluded (see *Appendix B – 1: List of studies excluded from literature review*) from the analysis as they:

- were single and multiple case design (10)
- reported on the effect of an intervention program (17),
- were clinical case studies (15),
- reported data on adaptive functioning, hand use or communication skills before regression (9),
- reported genetic findings (2),
- were review articles (2),
- reported on family wellbeing (1),
- examined the reliability of coding behavioural states (1),
- contained no empirical data (1),
- reported data on eye movements or motion analysis of hand movements (2), or
- could not be obtained, even through inter-library loan (1).

(See Figure 4.1 for a summary of the search results).

**Figure 4.1 Literature review search summary**



#### **4.4 Review findings**

Factors such as sample characteristics (age, sample size, diagnostic categories and clinical stage), measurement methodology, study design and genotype data were analysed.

##### *4.4.1 Sample characteristics*

Sample sizes in the 47 included studies ranged from 3 to 313 participants, with a collective total of 3,112 and a mean of 54.7 per study. In all but 8 studies, the gender of the participants was reported. All participants were female, except for one male. Age of participants ranged from one year to 55 years. Data on diagnosis and clinical stage of the syndrome were available in 21.7% (675) and 3.7% (115) respectively of the total sample. The vast majority (76.3%) of the 675 participants in studies where diagnosis was reported had a diagnosis of Classic RTT (N = 515), 3.7% (N=116) had Atypical/variant RTT, and 0.6% (N=4) a Congenital form of RTT (4.9% and 1.0% of the sample was reported to have an unknown and probable diagnosis of RTT, respectively). Where the data were reported (N=115), most study participants were in the later stages of the disorder (0.9% (1) in stage II, 77.4% (89) in stage III and 19.1% (22) in stage IV. In addition, three of the girls in one study were reported to be between stages III and IV).

##### *4.4.2 Measurement Methodology*

Measurement instruments adopted varied according to the behaviour(s) explored. Standardized behavioural scales and cognitive assessment scales were used in studies exploring autistic features, hand stereotypies, communication abilities and surveys exploring the behavioural characteristics of the syndrome. Direct and video

observations were used in 8 studies to support and describe the target behaviour(s) assessed through standardised measurements. Neurological studies exploring breathing abnormalities and sleep disturbances adopted standard medical monitoring such as polygraphic monitoring, EEG, ECG and visuafluoroscopy to assess respiration, brain activity and heart rates. A table setting out the measures used in the reviewed studies is included at *Appendix B – 2: Standardised measures used in Rett syndrome behavioural phenotype studies*.

#### *4.4.3 Study Design*

The majority of studies (70.7%) adopted a cross-sectional design. Two of the 47 studies analysed longitudinal data and one adopted a retrospective design by asking questions about the past.

### **4.5 Description of behavioural characteristics associated with RTT**

This first part of the review will focus on studies that described behaviours potentially associated with RTT. Behavioural characteristics described in the studies reviewed were: autistic features, breathing abnormalities, communication and language difficulties, cognitive skills, hand stereotypies and self-injury. Two types of paper were identified. The first analysed behavioural and emotional characteristics of the phenotype comprehensively. There were four such studies. The second investigated a single behaviour or cluster of behaviours. There were 14 studies of this type.

Table 4.1 shows the prevalence of behavioural and emotional features explored in the first type. Hand stereotypies were reported as occurring amongst all or nearly all of the sample but only in two of the four studies. Breathing abnormalities (hyperventilation and breath holding) were reported as common in all four studies (among 32-73%). Also

reported as occurring with high frequency in three of the four papers were fear or anxiety (among 68-75%), sleeping problems and night waking (among 51-77%), night screaming/laugh (among 39-84%), screaming, crying or laughing (among 77-84%) and self-injury (among 48-73%). Although self-injury is not part of the diagnostic criteria for RTT, the reporting of the behaviour in three of the studies highlights the issue that SIB is often present in the RTT sample. Categories of SIB identified were: biting fingers and hands, chewing fingers, hand to head banging, hand to object banging, hair pulling, scratching, bruxism, hitting the face, poking fingers in the eye and rubbing hands until the skin comes off. Changeable mood, low mood and crying for no reason were reported in two of the studies among about two-thirds. Both Coleman and colleagues (1989) and Samson and colleagues (1993) identified episodes of fear or low mood related to environmental changes.

**Table 4.1 Prevalence of behavioural and emotional characteristics in RTT**

Authors and sample size	Behavioural and emotional characteristic	Percentage of sample with characteristic
Coleman et al. 1988 (N=63)	Hand movements	100
	Teeth grinding	95
	Screaming	84
	Wake during the night, laughing	83
	Facial grimacing	76
	Inappropriate fear	75
	Sleeping problems	74
	Staring at light	67
	Inappropriate worry of crowds and noises	67
	Protrusion of the tongue	65
	Hyperventilation	63
	Breath hold	57
	Self-injury	49
	Hyperactivity	37
Samson et al. 1993 (N=107)	Night time laughing	84
	Anxiety	75
	Episodes of low mood	70
	Crying for no reason	62
	Crying during night	58
	Self-injury	48
	Night Screaming	48
	Mood changes	39
	Hyperventilation	32
Cass et al. 2003 (N=87)	Hand stereotypies	97
	Scratches self (n=63)	73
	Pointing with eyes (n=83)	66
	Hyperventilation (n=83)	60
	Breath hold (n=83)	41
Halbach et al. 2008 (N=53)	Night unrest	77
	Breath hold	73
	Anxiety	68
	Mood changes	66
	Agitation	54
	Awake during the night	51
	Air swallowing	41
	Apnea	38
	Hyperventilation	39
	Night screaming	39
Eye pointing	13	

The second type of study focused on a single behaviour or cluster of behaviours.

These are summarised in a Table included at *Appendix B - 3: Summary of behavioural and emotional characteristics of RTT*. Communication and cognitive abilities were most commonly investigated (9 studies) followed by breathing abnormalities (2 studies), autistic features (2 studies) and hand stereotypies (1 study). Eye gaze/eye pointing was

the communicative act reported in nearly all studies exploring communication and cognitive skills. Breathing abnormalities such as apnea, hyperventilation and breath holding were also consistently reported as being a feature of RTT. Hyperventilation was also included as being a form of communication. Screaming, anxiety and sleep problems were reported as frequent. Both eye contact and breathing abnormalities are part of the supportive criteria for RTT. Autistic features were reported in two studies. Items analysis for the DBC-ASA indicated that truly autistic behaviours were frequent in less than 50% of the individuals, but more frequent were behaviours associated with ASD and ID such as poor attention span, laughing and giggling without apparent reason and making non-speech noises.

In summary, the frequency of occurrence of several classes of behaviour suggests a distinctive behavioural phenotype. However, none of the studies identified in this part of the review had a control group and, therefore, it is not possible to establish the extent to which the behaviours that are predominant in RTT are characteristic of RTT per se or a reflection of the general severity of ID associated with RTT. These papers identified the potential elements of a behavioural phenotype but comparison to a control group is required to establish whether they are distinctive of RTT or more general features of severe ID. The next part of the review will summarise studies that had a control group to attempt to identify behaviours more likely to be exhibited by individuals with RTT.

#### 4.6 Studies with control groups

Eighteen studies had a control group (Tables 4.2-4.6). Comparison groups included individuals with:

- severe and profound ID with different diagnoses that included hereditary progressive dystonia, organic brain damage, cerebral palsy, Down syndrome, tuberous sclerosis, autism and Angelman syndrome (five studies),
- a specific aetiology: autism (six studies), organic brain damage (three studies), Fragile X syndrome (one study) and hereditary progressive dystonia (one study).
- non-disabled healthy participants.

Behavioural characteristics explored comprised: autistic features (7 studies), breathing abnormalities (5 studies), behavioural and emotional difficulties in general (4 studies), and sleep disturbances (3 studies).

Studies focused on autistic features (Table 4.2) explored the occurrence of specific behaviours associated with autism (Mazzocco et al. 1998), the differentiation and similarities between RTT and autism (Olsson 1987; Percy et al. 1988) and behavioural patterns specific to RTT (Mount et al. 2003b; Olsson and Rett 1985, 1987). Generally there was agreement in reporting behavioural characteristics which differentiate RTT and autism. Hypoactivity and slow movements, uniform stereotypic movements of the hands, hand stereotypies (i.e. hand washing, hand mouthing, hand together), reduction of hand function, broad based stance, hyperventilation, breath holding, ataxia, smiling, laughing and prolonged eye contact with familiar/unfamiliar people, no language or at most only two words and attainment at most of only the third stage of sensori-motor intelligence (Piaget) were only observed in the RTT group (Olsson and Rett 1985, 1987; Percy et al. 1988). Children with RTT appeared to enjoy social contact more and

eye contact with another person, smiling and looking at faces were observed in most of the cases with RTT. Moreover a restrictive repertoire of movements of the hands and fingers when manipulating objects was observed in children with RTT. Gaining noise from a paper bag seemed to be the only stereotypical manipulation of an object observed in the RTT group; it appeared to be the noise of the paper bag that made the children play with it rather than the manipulation itself (Olsson 1987). However similarities were also observed. Behaviours observed in both groups included lack of eye contact, empty gaze, teeth grinding, lack of social initiative, sleep problems, contentment when left alone, overreaction to sounds, lack of imaginative play and limited range of interests (Gillberg 1987; Olsson and Rett 1985, 1987; Percy et al. 1988).

**Table 4.2 Studies exploring Autistic features in RTT (percentages are reported where available)**

Authors	Sample characteristic		Methods	Design	Findings
	RTT	Control group			
Olsson and Rett 1985	24 female Age 1.10-20.11 yrs	13 Autism and 12 brain damage with autism age between 6 and 20.11 month	Observation of responses in acoustic, visual, tactile and gustatory stimuli and social contact.	Observation	Slow movements and hypoactivity, slow and uniform stereotypic movements, stereotypic hand washing, hand mouthing and hand together, consistent stretching and flexing of the finger, hyperventilation and time spent looking at objects and people $\geq$ time spending handling objects were observed most exclusively in the RTT group. Behaviour characteristic of children with autism (Rich stook movement, Swiftly alternating movements, Self-injury, Stereotypies, i.e. tics, repetitive movements, vocal stereotypies, Less social behaviour) were not observed in the RTT group.
Olsson 1987	27 female Age 1.10-14.11 yrs	ASD Organic Brain Damage (BD)	Presentations of 10 different stimuli to assess: sensory - motor performance, speech, stereotypes and self injuries and social reaction	Observation	There were qualitative differences in all RTT girls in regard to autistic traits. The RTT group smiled at familiar and unfamiliar person at about the same frequency. It also appeared that the children enjoyed social contact more than any thing else. In the sensorimotor and speech area, the children seem to look at the object presented only for short time and handling a paper bag was the only stereotyped movements observed in the RTT group. Children with ASD and BD had Complex hand and fingers movements (AS) and Good eye-hand coordination
Olsson and Rett 1987	27 female Age 1.10 – 14.11 yrs	18 Infantile autism and 18 organic brain damage with autistic traits	Observation in 10 stimulus situation to assess: sensory - motor performance, speech, stereotypes and self injuries and social reaction	Observation	Follow up of previous study. Behaviours observed in most RTT cases: smile or laughing, eye-contact and excitement when approached by another person, monotonous and uniform hand movements and restricted movements of the hands, bringing of the hand in front of the chin or chest, stretching and flexing of fingers, hypoactivity. Behaviours observed in all RTT children: at most two words, no social defence, time spent looking at objects long as time manipulating it, broad based stance, no self-injury, ataxia. Observed in both children with RTT and ASD: blank expression when looking at person, teeth grinding, hyperventilation, broad based stance and apraxic gait.
Percy et al. 1988	15 children Age 3-14 yrs	7 children (6 male 1 female with Autism age range 3.6-9 yrs)	Motor-behavioural checklist. Video observation in structured and	Cross sectional	A clear difference between children with RTT and autism was depicted. Respiratory pattern, ataxia/apraxia, slow movements and hand function occurred most exclusively in children with RTT, compared with behaviours such as overactivity, inappropriate vocalisation and complex repetitive movement found most

			unstructured settings.		exclusively in children with infantile autism.
Mazzocco et al. 1998	12 female 24 yrs	11 female with ID age test between 4 and 21. Comparison interview with the FX based on the (14 male) group to address qualitative differences.	Wechsler Semi-structured interview with the FX based on the 16 behavioural criteria for ASD.	Cross sectional	Qualitative differences between the RTT, Fragile X and comparison group were found. RTT female were reported as not having imaginative play (83%), all displayed stereotypic movements, and limited range of interest (92%).
Mount et al. 2003b	15 female Age 11-18 yrs Classic RTT	14 SMR	Parents interview VABS ABC	Cross sectional	Both group score below the floor in the VABS (mean ABS in months was 12.4 for the RTT group and 16.7 for the control group). The RTT group scored significantly higher than the control group in ABC (mean 63.5 and 46.3). Although 40% of the RTT sample score above the clinical cut off in the ABC this was not statistically significant. Sensory subscale RTT>SMR Relating subscale RTT>SMR

Breathing abnormalities were consistently reported in all studies to be a feature of RTT compared to a control group (Table 4.3). Hyperventilation, periodic apnea, and valsalva manouvre were observed in subjects within the RTT group and in none of the controls (healthy volunteers). All except one study reported episodes of hyperventilation, apnea and valsalva during wakefulness. More breathing abnormalities were observed in RTT group during the night, with the RTT group having a higher respiration rate than the controls (Weese-Mayer et al. 2008).

**Table 4.3 Studies exploring breathing abnormalities**

Authors	Sample characteristic		Methods	Design	Findings
	RTT	Control group			
Glaze et al. 1987	11 female Age 2-15 yrs	2 groups of healthy control (female and male): 12 subject age 2-5 yrs and 24 subject age 5-15	Polygraphic recording and videotaped observation of the motor activity.	Cross-sectional	The younger group (<5 yrs) had a significantly increased of sleep in stage 2 and decrease sleep latency. Percentage of total sleep time was reduced in the older group (>5) compared to the control group. In both groups, percentage of REM sleep decreased compared to the control group.
Marcus et al. 1994	30 female Age 1-17 years	30 female with primary snoring Age 1-32 years	Questionnaire (17) Polysomnography	Cross-sectional	RTT subject had episode of hyperventilation during wake, but all except one had episode of central apnea during REM sleep compared to control group.
Southall et al. 1988	18 Subjects 6-17 yrs	Healthy subject between the age of 4 and 15.	Recording of respiratory functions.	Cross-sectional	Hyperventilation is a primary problem and not a consequence of hypoxaemia. Breath holding and Valsalva were seen in 14 patients. During sleep hyperventilation, apnea or valsalva were not detected.
Julu, et al. 2001	47 female 2-35 yrs	11 female volunteer, age 5-28	1 hour non invasive autonomic and respiratory monitoring	Cross-sectional	Breathing pattern changed with age: apneustic and forceful breather were most seen in children under 5 and Valsalva manuvre and most normal breathing patterns were seen in the older group. Vacant spells were associated with involuntary movements and dystonic movements but not associated with epileptform discharges.
Weese-Mayer et al. 2008	47 female Age 2-7 years	47 healthy female matched for age, gender, ethnicity, age 2-7 years	Continuous respiratory recording at home during the night and ECG for 2 nights.	Cross-sectional	The breathing and heart rate during the night were irregular. The respiratory cycle length was shorter, mean AMP/Ti, increased breathing frequency and heart rate, decreased AMP.

Mount et al. (2002b) compared the behavioural and emotional features of RTT and females with severe ID, in the course of developing the Rett Syndrome Behavioural Questionnaire (see Table 4.4). Between-group analysis showed that the RTT group scored higher in items related to the hand (effect size 2.24) and breathing abnormalities (effect size 1.84). In addition, behaviours such as fear/anxiety and abrupt change in

mood were specific to RTT. Fear/anxiety, screaming, crying/laughing at night - time, facial grimacing and repetitive mouth/tongue movements were more frequently reported in the RTT than control group. Matson et al. (2008) also found that items related to the hand, such as restricted hand movements and inability to grasp purposefully were more frequent in an adult RTT group than a control group of adults with severe ID and autism. Mount et al. (2003a) found that 36.2% of an RTT group and 33.8% of a control group comprising individuals with severe and profound ID of mixed aetiologies, had a score of clinical significance in behavioural and emotional disturbances measured with the Developmental Behaviour Checklist (DBC). Although there was not a significant difference between the two groups in behavioural and emotional difficulties, the RTT group had a higher score on the Autistic-Relating and Self-Absorbed subscales. Further item analysis of the Autistic-Related subscale highlighted differences between the RTT group and children in the control group diagnosed with autism. The autism group scored higher on items reflecting core symptom of autism such as being aloof, avoiding eye contact and resisting cuddling, whereas the RTT group scored higher on items reflecting sleeps disturbances, unhappiness and being underactive. Moreover the RTT group had a lower score on the disruptive subscale, probably due to the fact that girls with RTT are less physically able than the control group. Mount et al. (2002a) found that the RTT group scored consistently lower on the Irritability, Hyperactivity and Inappropriate Speech subscales of the Aberrant Behavior Checklist (ABC) compared to a normative sample of adults with ID. However, the RTT group had a higher score on the Stereotypic behaviour subscale compared to females with ID and adults with severe ID, but not to adults with profound ID. It is possible that the community version of the Aberrant Behavior Checklist cannot differentiate the characteristic hand stereotypies of

RTT from other stereotypes displayed by individuals with profound ID (Mount et al. 2002a).

**Table 4.4 studies exploring behavioural and emotional characteristic**

Authors	Sample Characteristics		Measures	Study design	Findings
	RTT	Control group			
Mount et al. 2002a	50 female Age 19.08-33.66 yrs	Normative ABC-C sample.	Postal questionnaire ABC-Community version.	Cross sectional	RTT girls scored consistently lower in the Irritability, hyperactivity and Inappropriate speech subscale compared to the normative sample. Although the RTT group scored higher in the stereotypic behaviour and Lethargy subscale, these were not significant.
Mount et al. 2002b	143 female Age <19 yrs 123 Classic 20 Atypical/variant	85 female with severe/profound ID	RSBQ	Cross sectional	Analysis indicated that the scale discriminated behaviour more frequent in the RTT than in the control group. In particular, hand behaviours and breathing problems were more frequent in the RTT group
Mount et al. 2003a	143 Female Classic (123), Atypical (13) and probable (7) Age <18 yrs	85 girls Severe/Profound ID.	DBC Questionnaire	Cross sectional	Behavioural and emotional difficulties were identified in 36.2% and 33.8% of the RTT group and control group. No significant difference was found between the RTT and control group in the subscales, except for the autistic subscale (mean 9.09 compared to 4.40). Analysis revealed that the RTT and autism group differed on items reflecting core symptoms of autism.
Matson et al. 2008	6 female Age >18 yrs	ID and Autism (n=6) Group selected to match age, sex, level of ID and verbal ability.	ASD-BPA VABS RSBQ MESSIER	Cross sectional	In the ASD-BPA significant differences were found between the RTT and ASD group in items such as aggression, repeated vocalisation, and playing with own saliva. These were more frequent in the ASD group. In the socialisation domain (VABS) significant difference appeared between the ASD and control group in imitation simple movement, addressing familiar people by name and sharing. No significant difference appeared in the RSBQ between groups, although the RTT group showed higher rate in hand skills and restricted repertoire of movements.

In children, total sleep time and day - time sleep decrease with age. Comparison of sleep disturbances with a normative group highlighted that total sleep time among

females with RTT does not decrease with age. Ellaway et al. (2001) investigated the sleep patterns of a group of females with RTT for seven consecutive days and nights. They found that there was a lack of decreased sleep typical of normal children in the RTT group and suggested that sleep disturbances were the result of an arrested brain development. Piazza et al. (1990) found that females with RTT had more inappropriate day - time sleep and decreased night - time sleep compared to a group of age peers. Results indicated that the RTT group had significantly more total sleep, less night sleep and inappropriate day sleep. Similarly, comparison with a group of children with early infantile autism indicated that abnormalities in the sleep-wake cycle persisted into older age in the RTT sample, and environmental and pharmacological intervention was not as successful. In the autism group, abnormalities in the sleep-wake cycle were only observed in early childhood and improved following intervention (Segawa and Nomura 1992).

**Table 4.5 Studies exploring sleep problems**

Authors	Sample characteristic		Methods	Design	Findings
	RTT	Control group			
Piazza et al. 1990	20 female Age 1-32 yrs	Normative sample	Momentary time sampling to measure the sleep-awake pattern over 24 hr	Cross-sectional	Increased total sleep time compared to age matched peers, less night-time sleep and more day sleep. Night-time sleep decreased with age and day sleep increased with age.
Segawa and Nomura 1992	8 female 1-14 yrs	Early Infantile Autism (EIA) and hereditary progressive dystonia (HPD)	Polysomnographic. Recording of Sleep-wakefulness cycle.	Cross-sectional	Sleep-wakefulness cycle was disturbed in both RTT and EIA group with the difference that in EIA these abnormalities were observed only in early childhood, while in the RTT group these abnormalities were observed in the late childhood in cases after the age of 10 yrs.
Ellaway et al. 2001	83 female 4-40 yrs	Normative data from normal children.	Sleep diary to report periods of sleep and wakefulness for 7 days.	Cross-sectional	Sleep latency was significantly different between age group. Subjects with seizure had more day sleep and those able to walk had less day sleep and more sleep efficiency than those who could not walk.

#### **4.7 Phenotype-genotype association**

Eleven studies investigated the relationship between genotype variation and phenotype (see Table 4.6) in terms of: behavioural features as measured by the RSBQ (Robertson et al. 2006), sleep disturbances (Young et al. 2007), hand stereotypies (Carter et al. 2009; Charman et al. 2005; Neul et al. 2008; Temudo et al. 2008, 2007; Vignoli et al. 2009), early diagnosis of autism (Young et al. 2008) and severity of autistic behaviours (Kauffman et al. 2011).

Mutations reported by most of the studies were R270X, R255X, R133C, R306C, R106C, T158M, R168X, and R294C. One study simply reported type of change (Missense or Truncating) and another compared samples with and without a positive *MECP2* mutation. There is now evidence that variability in behavioural manifestation and clinical severity can be linked to the type of mutation. For example, using the RSBQ (Mount et al. 2002b), Robertson et al. (2006) suggested that cases with the ‘milder’ genotypes, such as R133C, R294X and R306C, were more likely to have a higher score in domains relating to fear/anxiety, mood and body rocking.

The relationship between clinical severity and type of mutation with autistic behaviour was the focus of 3 studies. Kaufmann and colleagues (2011) reported that greater clinical severity and low level of adaptive skills had no effects on severity of autistic behaviour, measured with the Screen for Social Interaction (SSI). Moreover no differences were found in autistic behaviour between groups of mutation, although less severe autistic behaviour was found among those with T158M and R270X mutation, linked with a more severe clinical phenotype, and cases associated with milder phenotype such as R133C, R294X presented with more severe autistic behaviours. R306C and T158M were more likely to have had an early diagnosis of autism (Young et

al. 2008). These individuals presented with a milder phenotype and were more likely to have some functional use of the hands and to be ambulant.

Data from this review suggests that subjects with R294X, R306C mutations and large deletions had the highest probability of sleep problems. Individuals with R306C mutation were found to have the highest severity of sleep problems (Young et al. 2007). Cases with a severe phenotype, R270X, T158M, R106 and R255X, had the highest probability of day sleeping (Robertson et al. 2006; Young et al. 2007). Patients with R270X, associated with a more severe phenotype, were more likely to exhibit stereotyped hand behaviours and cases with the R294X mutation were found to be less likely to have hand behaviours by Robertson et al. (2006), but a high percentage of subjects with this mutation were described as having frequent hand stereotypies by Carter and colleagues (2009) and Vignoli and colleagues (2009), who described stereotypies in this group of subjects as severe. Overall, R306C and early truncating mutations were associated with more frequent hand clapping and T158M, R294X and C-Terminal deletions with hand wringing (Carter et al. 2009). Charman et al. (2005) reported that cases with early truncating mutations had higher scores in the hand stereotypies domain of the RSBQ, particularly associated with R270X and R255X among the common mutations. Neul et al. (2008) reported a less severe phenotype in relation to hand use, in cases with R294X, R133C and C-terminal compared with R168C and large deletion mutations.

Types of stereotypies were also investigated. Washing/clapping/wringing, and mouthing with hands together were the movements most often described; mouthing with hands apart was described in all the studies, followed by flapping, tapping, hair pulling and hand gaze. Carter and colleagues (2009) identified 15 different categories of hand stereotypies in a large sample of 144 female with RTT. Wringing, mouthing one

hand and clasping one hand were the topographies more frequently observed with subjects having a median of two hand stereotypies. Similarly wringing of the hands was the stereotypy most often observed by Temudo et al. (2009). Other topographies of stereotypies such as head rolling, trunk rocking, head repropulsion and bruxism were also observed in the majority of the sample (Temudo et al. 2009, 2008). Hand clapping was described to be more frequent in the R306C and early truncating mutations. Single hand mouthing was more frequently reported in those with R306C and C-Terminal mutations. All cases were described to have constant or frequent hand movements, however those with R294X and C-terminal had constant stereotypies (Carter et al. 2009). Although the movement disorder is described in all subjects, frequency, severity and number of the stereotypies decreased with age, possibly due to increased rigidity and tremor (Carter et al. 2009; Temudo et al. 2009, 2008; Vignoli et al. 2010).

Language abilities were found to be preserved more in those cases with a milder mutation (R294X and R133C, Uchino et al. 2001; Neul et al. 2010).

In general, although some differences have been described between single mutations, with milder phenotypes displaying behaviours relating to anxiety, autism and changes of mood and severe phenotypes having behaviours related to the hands and day sleep, relationships are weak due to small sample sizes which reflect the rarity of RTT as a condition (Robertson et al. 2006) and the differing methodologies and severity scales employed. How much variability is to be accounted by the genotype is still to be determined, albeit some studies have reported minimal differences between individuals with and without a *MECP2* mutation (Carter et al. 2009; Temudo et al. 2007, 2008; Vignoli et al. 2009).

**Table 4.6 Genotype - phenotype association studies**

Authors	Sample	Measures	Design	Genotype data	Behaviours	Findings
Robertson et al. 2006	135 subjects 2.4 to 27.4 yrs (>19 excluded from comparison study)	RSBQ	Cross sectional	MECP2 (100%)	Behavioural problems	Significant differences emerged between the UK and ARSD cohort in the hand behaviour, body rocking/expressionless face and face movements. Mean score in RSBQ differed between mutation, but was not significant. Cases with R294X, R133C and R306C experienced more problems in mood, fear/anxiety and body rocking. R270X, R255X experienced more severe hand stereotypies.
Kauffman et al. 2011	80 female Age 1.6 – 14.9 yrs	RSBQ VABS SSI RSSS	Cross-sectional	MECP2 (100%)	Autistic features	Age was found to be predictive of increased clinical severity, lower adaptive and social skills but not of behavioural problems. Greater clinical severity was correlated with a lower adaptive and social skills and higher RSBQ total score. Better social skills (SSI) were associated with lower behavioural problems (RSBQ), but social skills (VABS) did not influence RSBQ score. Less severe autistic features were found in cases with T158M and R270X mutations and more severe autistic features associated with R133C, P168X, R255X and R294X.
Young et al. 2008	313 female Age 1.5-45 yrs	Questionnaires	Cross sectional	MECP2 (73.2%)	Autism	55 (17.6%) participants had an initial diagnosis of autism. These participants were more likely to have learned to walk or their mobility was above average at 10 months, have a less severe phenotype according to Kerr, Pineda and Percy score and be more likely to be ambulant, be able to finger feed and have retained some hand skills. Participants with R306C and T158M mutations were more likely to have had a diagnosis of autism.
Young et al. 2007	237 subjects 2-29 years	Questionnaire	Longitudinal and cross sectional	MECP2 (69.2%)	Sleep disturbances	Frequency of sleep problems was found to be high and to be more frequent in the younger group. Night laughing and teeth grinding at night were found to be more prevalent (58.9% and 54.9%). Cases with R294X and R306C mutation had the highest probability of sleep problems.

Vignoli et al. 2009	12 female 11 classic, 1 congenital Age 14-31 yrs	Observation of Video recording in clinical setting. Parental interview Neurological classification and video EEG polygraph recording.	Cross sectional	MECP2 (100%)	Hand stereotypies	Mean age of onset of stereotypies was 19.4 months, and the frequency described to be constant during wake and disappear during sleep. Hand mouthing, bruxism, pill rolling and twisting two-three fingers was present in 6/12 subjects.
Carter et al. 2009	144 female 2-31 yrs	Video recording. Questionnaire	Cross sectional	MECP2 (76.4%)	Hand stereotypies	Most common hand stereotypy was midline wringing (59% of all sample and 61.8% of those with positive mutation). Numbers of stereotypies decreased with age (32.5% of >19 had two or three different stereotypies). Over 90% of the subject had constant or frequent hand stereotypies. 58.3% of individuals with the R294X mutation and in 45.5% those with C-terminal mutation were described as having constant or frequent hand stereotypies.
Temudo et al. 2008	60 subjects 5-13 yrs.	Videotaped and development of clinical checklist.	Cross sectional	MECP2 (100%)	Hand stereotypies	Hand stereotypies were present in all subject, bruxism was present in 80% of the sample. Frequent of stereotypies was lower in the group with truncation mutation.
Temudo et al. 2007	83 subjects Classic (60.2%) and variant (39.8%) 1-31 years	Video recording and observation	Cross sectional	MECP2 (63.9%)	Hand stereotypies	Most frequent hand stereotypies observed was hand wringing of both hands in the midline (73.3% and 80% in respectively group I and II). Bruxism was present in 90% of the sample and was observed only during wakefulness. Stereotypies decrease after the age of 10 in particular in subject with positive MECP2 mutation.
Charman et al. 2005	240 females (RSBQ available on 169)	RSBQ BIRSS Severity score	Cross sectional	MECP2 (190 cases)	Hand stereotypies, clinical severity	Cases with Early truncation have higher severity score and higher hand factor in the RSBQ. Across the 6 most common mutation, cases with the R133C had later age of onset and lower score and cases with R168X, R270X and R306C/H showed a wider distribution. RSBQ score did not differ significantly across the 6 mutation groups.
Neul et al. 2008	245 female Classic RTT	Clinical assessment	Cross sectional	MECP2 (97%)	Language, ambulation and clinical severity	Total clinical severity score varied between mutation groups: cases with R133C mutation had a lower CSS, compared to cases with Large Deletion. Higher

					percentages of individuals with R133C, R294X and C-Terminal mutation with preserved ability to walk, use of words and hand use. Cases with Large Deletion and R164X presented with a more severe phenotype.
Uchino et al. 2001	99 females Age 3.6 to 29.9 yrs	Clinical assessment	Cross sectional	MECP2 (22.2%) Language development	Of the 22 cases with mutation in the MECP2, 4 spoke two words sentences (A201V, R294X, 269AaFS-28X, Deletion 259bp); 10 spoke words only and 6 had no words.

#### 4.8 Variation in expression by age

A few studies contained an analysis of phenotypic variation in relation to age.

Generally, there was agreement that adults with RTT had lower rates of behavioural problems compared to adults with autism (Matson et al. 2008) and lower scores on the irritability, hyperactivity and inappropriate speech domains of the Aberrant Behavior Checklist compared to the published normative data for adults with ID (Mount et al. 2002a). Halbach et al. (2008) reported better communication skills in an older RTT group compared to a younger group but Cass et al. (2003) found no differences in the cognitive skills of children and adults. Breathing abnormalities tended to improve in the adult and be more accentuated during childhood and adolescence (Cass et al. 2003, Julu et al. 2001). Agitation, mood changes, night screaming and sleep disturbances were more frequent in the older group (Halbach et al. 2008). Autistic behaviours, measured with the DBC –ASA, were more frequent in children (Wulffaert et al. 2009).

Studies differed with respect to the relationship between sleep problems and age.

Ellaway et al. (2001) found sleep did not decrease with age. In contrast Piazza et al. (1990) reported an increase in total sleep time, a decrease in night - time sleep and increased daytime sleep with age compared to a normative sample. Young et al. (2008) reported that night screaming, night teeth grinding, sleep talking and night terrors were

more frequent in the younger group and night time seizures and daytime sleeping were more frequent in the older group (>18 years).

#### **4.9 General discussion**

Autistic features in RTT have been reported in previous accounts to be characteristic of the syndrome, to the point that RTT is classified under the DSM IV as one of four specific Pervasive Developmental Disorders (PDD). The current classification manual is under revision and individuals with RTT will not be classified as PDD unless the person meets criteria for autistic spectrum disorder ([http://www.rettsearch.org/news\\_pubs.jsp](http://www.rettsearch.org/news_pubs.jsp)). This review points to an agreement in findings that, although both conditions present with social and communication difficulties and repetitive movements, qualitative differences are found in behavioural patterns and in the fact that RTT and autism differ in the core symptoms of autism. In addition, while development of communication skills is affected in autism, development of motor skills is not, whereas regression in language and motor skills are essential features of RTT. Loss of purposeful hand skills, poor coordination, ataxia, apraxia and loss of verbalisation represent the regression features of RTT. Stereotypical movements associated with autism are generally complex and often involve the manipulation of objects without the loss of pincer grip. Although the relationship between age, severity of the phenotype and diagnosis has been investigated in recent studies, it still remains to be analysed further. Younger children appear to display greater symptoms related to autism, confirming other findings that autistic symptoms persist after the regression stage. However, the relationship between clinical or behavioural severity and autistic symptoms is not clear cut. Contradictory results can be attributed to different study designs and measures and to the fact that only one study adopted a control group.

Breathing abnormalities most often reported were apnea, hyperventilation and breath holding. The focus of the studies was on the characterisation of breathing rhythm, respiratory patterns during sleep, hyperventilation, EEG and respiratory patterns. The majority of studies investigated respiratory patterns during wakefulness. Although several studies have confirmed that breathing abnormalities occur primarily during wakefulness (Cirignotta et al. 1986; Glaze et al. 1987), more recent studies have indicated that subtle abnormalities are also present during sleep. The mechanisms behind the irregular breathing patterns are still unknown and factors other than organic ones may be associated with breathing irregularities. Mouse model studies indicate that individuals with RTT suffer from a deficiency in noradrenergic and serotonergic modulation in the respiratory network (Rohdin et al. 2007) and studies of physiology indicate that breathing abnormalities are caused by brain immaturity (Julu et al. 2001). Studies that included a control group indicated that breathing abnormalities were more frequent in the RTT group. However, control participants in all studies were healthy subjects (participants were matched for age, gender and ethnicity in only one study, but not for level of ID). Therefore, the specificity of breathing abnormalities to RTT among people with severe/profound ID has yet to be established.

Stereotyped hand movements were present in all or nearly all cases and related to restricted hand movement and purposeful grasping. It is thought that the stereotypies have an organic aetiology independent of environmental manipulation, albeit that a possible role for environmental influences as well as the individual's internal state in the frequency of hand stereotypies is mentioned in several studies (Kerr et al. 1987; Temudo et al. 2008; Vignoli et al. 2009) but with discordant findings. However, there have been no empirical reports with a large sample size to explore this to date.

#### **4.10 Critical analysis and recommendations for future research**

As indicated by other studies, several limitations have been identified in behavioural phenotype studies. These include: absence of well-chosen comparison groups, small sample sizes, absence of standardised assessments and lack of clear definition of behaviours assessed. Studies included in this review employed different assessment methods and in the case of neurological studies (concerning sleep and breathing) short-term assessments were generally used. Most studies investigating sleep dysfunction and breathing abnormalities recorded sleep or breathing during a 24-hour period; only one study (Ellaway et al. 2007) recorded sleep over 7 days and only one (Rohdin et al. 2007) reporting breathing abnormalities over 7 days. Methods of recording sleep included parental questionnaire, sleep diary, polysomnographic recording and momentary time sampling to record sleep-wake patterns. Sample sizes employed by all but two studies were small. Overall, the studies adopted cross sectional designs with only a few describing behavioural features over time. There are limitations in the use of cross sectional studies. They provide data on the frequency of the behaviour at a given time, but are inadequate to explore behavioural change given ageing.

As Mount and colleagues (2003a) highlighted, no published literature had employed a comparison group or standardized assessment to measure behavioural and emotional characteristics of RTT prior to their study on the behavioural phenotype of RTT. Several studies have used established assessment scales to explore the characteristics of RTT and, although these have provided useful descriptive data, only one scale in the English language has been developed to capture RTT specific behavioural features (RSBQ, Mount et al. 2002b). One limitation of the Mount and colleagues study is that data on the validation of the RSBQ is only available for the child group. Moreover, the scale is in need of a revision to reflect recent discoveries in the behavioural and clinical

phenotype of the syndrome and, as highlighted by Kaufmann and colleagues (2011), the influence of neurological and behavioural factors needs to be explored. And yet no between-group study to date has analysed RSBQ data from a large adult sample. Fabio et al. (2005) developed the Rett Assessment Rating Scale (RARS), though the scale has not yet been translated into English.

The main focus in the majority of studies exploring communication and cognitive skills was the level of impairment of the individual with RTT. Subjects were assessed using traditional standardised instruments, for which fine motor skills, in particular the hands, known to be impaired in RTT, are a pre-requisite. Hence, such traditional methods of cognitive assessment may be inadequate for individuals with RTT. It is possible that poor performance is interpreted as cognitive impairment, without taking into consideration the individuals' other difficulties. In addition, these studies have not used direct observation alongside the use of validated scales. Direct observation might be more sensitive to describe qualitative differences between groups. Another limitation is the general lack of research exploring the behavioural profile of adults with RTT. There is evidence in the literature that girls with RTT survive well into adulthood, however there are very few studies of girls with RTT within this age group and the majority are clinical case studies. Only 8 papers from this review included participants aged 40 years or older thus findings are difficult to generalised to the entire RTT population.

Although descriptive studies can identify potential elements of the RTT phenotype, a well chosen control group is needed to establish whether behaviours are specific to RTT or reflect level of ID more generally. Although some studies had a control group, these were not always chosen sufficiently well to control for the severe/profound physical and intellectual disability associated with RTT (e.g., studies with general ASD

or healthy comparison groups). Only one study has included a control group matched for age, level of ID, gender and verbal ability. However, its sample size was small (N=6) limiting the generalization of findings. Although the advantages of including healthy subjects in comparison studies have been highlighted in terms of pointing to strengths and weaknesses (Seltzer et al. 2004), it is not possible to know whether a behaviour in question is specific to a syndrome or a more common problem in individuals with similar level of intellectual disabilities without an appropriate control group (Mervis and Klein-Tasman 2004).

The study reported subsequently in this thesis includes a large sample of females with a definitive diagnosis of RTT. This review suggests that hand stereotypies and breathing abnormalities are established core features of RTT. The study to be described adopted a group matching design controlling for chronological age, adaptive skills, language ability and gender to explore other behavioural characteristics of RTT, including hyperactivity, depression, self-injury and repetitive behaviour.

## CHAPTER 5

### NATIONAL SURVEY METHODOLOGY

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#### **5.1 Introduction**

The previous chapters introduced RTT from a medical and genetic prospective and reviewed the literature on the behavioural phenotype of RTT. Communication and language abilities, autistic features, breathing abnormalities and stereotypies were the aspects of the RTT phenotype most commonly studied in the literature. Ages of participants varied from one year to 55 years with the majority of the studies including children. Only a small percentage of studies focused on adults. There was a lack of research on developmental trajectory into adulthood and there is a need for more studies which investigate the behavioural and emotional features of adults. Other limitations of the existing literature include the small number of participants in most studies and either the absence of a choice of a meaningful control group when attempting to establish the distinctive phenotype. Hence, this study aimed to gain a national sample of people with Rett syndrome and compare their characteristics with a well-chosen control group. This chapter describes the recruitment procedures, measures and statistical analysis used in the survey conducted.

#### **5.2 Inclusion Criteria**

The study began before the new diagnostic criteria for RTT were established (Neul et al. 2010). Thus participants selected for this study fulfilled the Hagberg et al. (2002) diagnostic criteria.

Participants included in the study have a clinical diagnosis of:

- a. Classic Rett Syndrome (regardless of *MECP2* mutation test result) **or**
- b. Classic Rett Syndrome incomplete<sup>1</sup> (regardless of *MECP2* mutation test result) **or**
- c. Atypical Rett Syndrome (with positive *MECP2* mutation test result).

Participants were also to be living in the family home. However, it was not known in advance that a small proportion of the included sample were living in accommodation other than the family home. Where these families completed and returned the questionnaire packs, the affected individuals have been included in the analysis of individual characteristics (N=11), but not in the relationship between individual characteristics and carer stress or mental health.

### *5.2.1 Ethical approval*

Before commencing the recruitment of participants for the study, ethical approval was received by Wales REC, application number: 09/MRE09/50. A copy of the approval letter can be found in *Appendix C – 1: “Ethical Approval letters”*.

Invitation letters were sent by the British Isle Rett Syndrome Survey and names and addresses of potential participants were unknown to the researchers until the families provided them.

## **5.3 Sampling frame and recruitment**

Families were recruited through the British Isle Rett Syndrome Survey (BIRSS). The BIRSS is the UK and Ireland Rett syndrome database held by Professor Angus Clarke and coordinated by Dr Ania Jarwoska at the Institute of Medical Genetics at

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<sup>1</sup> Where the diagnosis appears to be Classic RTT but some information (usually head circumference at birth) is unavailable

Cardiff University. In September 2010, the database held data on 933 patients (807 alive and 126 deceased). The BIRSS was established in 1982 by Dr Alison Kerr at Glasgow University and developed by her over more than 20 years. Following Dr Kerr's retirement in 2005, the BIRSS database was transferred to Cardiff University. The BIRSS is now the key resource for a research project entitled 'A Descriptive Study of Rett Disorder throughout Life: The British Isles Rett Syndrome Survey' (Principal investigator, Professor Angus Clarke) and is the national register of people who have been diagnosed with RTT. For each individual, data are collected on the health of the individual and the severity of the condition via a detailed Health Questionnaire (HQ) completed by families of patients. The database also includes additional clinical data gained in RTT clinics conducted in the past by Dr Kerr, ongoing clinics conducted in Cardiff, as a result of the above ongoing study and occasional post mortem reports (personal communication with Dr A. Jarwoska, September 2010).

In October 2009, a random sample of 150 individuals and families was selected from a sample of 364 who met the inclusion criteria for the study. The sample was stratified by age of individual into 4 age groups: 5-11 years, 12-17 years, 18-25 years and 26 years or over. Table 5.1 shows the number of cases in each age group who met the inclusion criteria in the BIRSS database and the number randomly selected from each for the study.

**Table 5.1 Number of participants in each age group randomly selected**

Age group	5-11 yr	12-17 yr	18-25 yr	26 yr +
No of patients	40	67	111	146
Stratified random selection	16	28	46	60

An invitation letter, containing an information leaflet, a consent form, assent form, prepaid envelope and prepaid card that families could return if they did not wish to participate in the study was sent to all but 16 of the families of identified individuals. In the case of those 16 families, the BIRSS did not have established contact with them (A copy of the invitation letter, leaflet, consent and assent form can be found in *Appendix C – 2: “Invitation letter, leaflet, consent and assent form”*).

Due to a low response rate (56 families (21.6%) returned a consent form), invitation letters were then sent to the families of the remaining 174 individuals who met the inclusion criteria (after excluding 33 families because their daughter with RTT lived in residential care and a further 7 families where there was no known means of contacting them). In total, 318 invitation letters were distributed to families of individuals meeting the inclusion criteria for the study. A follow up letter was sent to families who did not return the consent form or the card, two months after receiving the first invitation letter. The letter again contained an invitation letter, consent and assent form and a prepaid card to return to indicate unwillingness to participate in the study. The letter explained that they would not be contacted again.

A total of 126 families returned a consent form. 122 questionnaire packs with prepaid return envelopes were distributed (4 families were excluded because the RTT girls were living out of the family home). Families were contacted first by phone and then by letter if they had not returned the questionnaire packs within two months from receiving them. 13 families indicated that they did not wish to fill in the questionnaires and wanted to be removed from the list of participants. In a further 2 cases, invitation letters were returned because of an incorrect address. Ninety- three families returned

completed questionnaires (a response rate of 76.2%). Ninety-two participants with RTT were female and 1 male. The male participant was excluded from the final sample. 1 participant passed away during the study and was not included in the analysis.

#### 5.4 Control group

In collaboration with Prof. Chris Oliver at the Cerebra Centre, University of Birmingham, a sample of individuals with ID and a genetic disorder other than RTT was selected for comparison with the RTT group (see Table 5.2).

**Table 5.2 Genetic syndromes within the control group**

<b>Syndrome</b>	<b>Frequency (%)</b>
Angelman syndrome	25 (37.9%)
Cri du cat syndrome	5 (7.6%)
Cornelia de Lange syndrome	26 (39.4%)
Prader Willi syndrome	1 (1.5%)
Smith Magenis syndrome	2 (3.0%)
1p36	7 (10.6%)
All	66 (100%)

Only individuals with no verbal ability were included in the comparison study. Three individuals in the RTT group were excluded as they had preserved verbal ability (leaving a total of 89 individuals). In addition, groups were matched on gender (all female, which necessitated reducing the RTT sample from 89 to 88, chronological age and adaptive behaviour (feeding, dressing and washing). As none of the RTT sample could dress or wash independently or with support, the control group was selected to be similar in these respects. The RTT sample had some abilities in feeding although no-one could feed themselves independently. Again, the control group was selected to be as

similar as possible. Table 5.3 sets out these basic parameters of the RTT and control groups.

**Table 5.1 Matching characteristics of the RTT and control groups**

Groups	Gender	Chronological age Range (mean, SD) (years)	Feeding Not at all	Feeding with help
RTT (n=88)	F 100%	4 - 47 (20.28; 10.20)	55 (62.5%)	33 (37.5%)
Control (n=66)	F 100%	4 - 45 (15.00; 10.02)	21 (31.8%)	45 (68.2%)

## 5.5 Measures

Families were asked to complete two questionnaire packs, each containing 12 informant-based scales (Although the initial survey included 12 assessment scales of child behaviour and 12 scales for the family, this study has included the analysis of 9 measures of child behaviour and 5 measures of family psychological well-being).

The first pack contained measures relating to the person with RTT, covering their early development, current skills, behavioural characteristics, medical problems and depression. The second booklet contained measures relating to family member's stress, level of anxiety and depression, positive experiences, level and experience of support received in the past and at present, perception of improvement or deterioration of their RTT family member over time and the experience of siblings.

After parents returned the completed questionnaire packs, the Vineland Adaptive Behavior Scale – Survey Form (VABS: Sparrow, Balla and Cicchetti 1984) was carried out as a telephone interview with one of the parents.

A copy of the questionnaire packs can be found in *Appendix C – 3: Questionnaire packs*.

## ***5.5.1 Measures relating to the Child/Adult with Rett Syndrome***

### *5.5.1.1 Demographic information*

Information was requested about date of birth, age of diagnosis, who diagnosed the condition, whether or not a genetic cause of RTT has been identified and height and weight to calculate BMI.

### *5.5.1.2 RTT development*

The questionnaire contained questions about early development and current abilities based on the diagnostic criteria for RTT (Hagberg et al. 2002) and some questions from the BIRSS questionnaire. Information was sought about pregnancy, delivery, early development of the child, head growth, regression and existing abilities.

### *5.5.1.3 Severity Score (Smeets et al. 2009)*

In this simplified severity score, 6 features of RTT (sitting, walking, hand use, speech, epilepsy and spine deformation) are examined. Each domain is scored from 0 to 3, where 0 indicates a normal situation, 1 indicates impaired ability to sit and walk, reduced hand use, some words, epilepsy is controlled with medication and scoliosis is mild; 2 indicates that the abilities to sit, walk, use hands and speak are lost, epilepsy is uncontrolled and scoliosis is severe; 3 indicates that the individual never acquired the abilities to sit, walk, use hands and speak, status epilepticus occurs and scoliosis has been operated upon. The severity score evaluates the overall severity of the syndrome and indicates domains that are considered to influence evolution and severity in the long term. However, it is not sensitive to progression of the syndrome over time. The maximum score is 18. Cases with a score less than 9 are considered mild or less severe.

#### *5.5.1.4 Health questionnaire (Hall et al. 2008)*

This contains two series of 15 possible medical problems. In the first, the respondent is asked to rate whether the person with RTT has ever suffered from any health problems and if so whether the person had any treatment (Have these problems ever affected your child? i.e. gastrointestinal problem, epilepsy, bowel problem etc.). In the second, the respondent is asked to rate whether the person has had any of the medical problems in the last month (Have these medical problems affected your child in the last month?). Each problem is rated from 0 (never) to 3 (severe). An Overall Health Score is obtained by summing the total for the health problems during the person's life and during the last month. Inter-rater reliability was 0.72 for health problems occurring in the person's life and 0.76 for the health problems in the last month (Hall et al. 2008).

#### *5.5.1.5 The Activity Questionnaire (AQ)*

The AQ (Burbidge et al. 2010) is an informant-based questionnaire that measures the frequency of impulsivity and overactivity behaviour in children and adults with ID, with and without verbal communication and mobility. It contains 18 questions (i.e. Does your child wriggle or squirm about when seated or laying down? Does your child find it difficult holding still?) rated on a 5-point Likert scale, where 0 indicates never or almost never, 1 some of the time, 2 half of the time, 3 a lot of the time and 4 always or almost all the time. Behavioural features are clearly described and the respondent is asked to rate the frequency of each behaviour in the last 4 weeks. The scale is divided into three subscales: Overactivity, Impulsivity and Impulsive Speech.

Immobile and non-verbal individuals are scored differently from those who can walk and/or speak. Scores on the Impulsivity subscale for non-mobile individuals are pro-rated in order to compare with those for mobile individuals. Total scores on the

subscale for immobile individuals are multiplied by 1.5 in order to compare them to the total scores for mobile individuals. Total scores are 60 and 72 for immobile and mobile individuals respectively. Scores of 32 and 24 (<18 years) and 26 and 22 (> 18 years) in the Impulsivity and Overactivity subscales were identified as abnormally high (Burbridge and Oliver 2008, cited in Oliver et al. 2011). Item level inter-rater reliability ranged from 0.31-0.75 (mean 0.56) and test re-test reliability ranged from 0.60-0.90 (mean 0.75). Internal consistency was good (Burbidge et al. 2010).

#### *5.5.1.6 Mood, Interest and Pleasure Questionnaire Short-Form (MIPQ-S)*

The MIPQ-S (Ross and Oliver 2003b) assesses mood, interest and pleasure levels in individuals with severe and profound ID. It contains 12 items scored using a 5-point Likert scale based on the respondents' observation of the participant in the last two weeks (i.e. In the last two weeks, how often did you hear positive vocalizations when your child was engaged in activities?). The scale is divided into 2 subscales: Mood and Interest and Pleasure. High scores in the total scale score and subscales indicate high interest and pleasure and positive mood. Scores of 6 and 15 ( $\leq$  18 years) and 6 and 13 (>18 years) were identified as being abnormally low and 23 and 24 ( $\leq$  18 years) and 21-24 (<18 years) have being identified as being abnormally high for the mood and Interest and Pleasure subscales (Ross et al. 2008, cited in Oliver et al. 2011). Inter-rater and test-retest reliability of the scale was good (0.85 and 0.97 respectively) as was internal consistency (Cronbach's alpha coefficient Total= 0.88, Mood= 0.79, Interest and Pleasure= 0.87) (Ross and Oliver 2003b).

#### *5.5.1.7 Rett Syndrome Behavioural Questionnaire (RSBQ)*

The RSBQ (Mount et al. 2002a) is a checklist developed to assess behavioural and emotional characteristics of RTT. It contains 45 items designed to measure severity of the behavioural phenotype in RTT (i.e. there are times when breathing is deep and fast, spells of screaming for no apparent reason during the day). Items are rated 0 to 2, where 0 indicates that the behaviour is not true, 1 sometimes true and 2 often true. The scale is divided into eight sub-domains: General Mood, Breathing abnormalities, Hand behaviours, Repetitive face movements, Body rocking and expressionless face, Night-time behaviour, Fear/Anxiety and Walking/Standing. Internal Consistency was high (>0.90) for the RSBQ Total Score and for the 8 subscales (0.60-0.79). Inter-rater reliability and test-retest reliability were good (RSBQ Total Score = >0.80; subscales = 0.60 - 0.79)

#### *5.5.1.8 Challenging Behaviour Questionnaire (CBQ)*

The CBQ (Hyman et al. 2002) is an informant-based scale that assesses the presence and frequency of self-injury and aggressive behaviour. Respondents are asked to rate the presence of self-injury and aggression in the last month and to specify the topography of the self-injurious behaviour (hitting self, bites self, slap, bangs head, pulls hair or skin, rubs or scratches self, inserts finger or objects in self). Psychometric properties of the scale are considered to be good with good inter-rater reliability (reliability coefficients ranging from 0.61 to 0.89) (Hyman et al. 2002).

#### *5.5.1.9 Repetitive Behaviour Questionnaire (RBQ)*

The RBQ (Moss et al. 2009) is a 19 item informant-based scale used to assess repetitive behaviour in individuals with ID. The scale is divided into five subscales:

Stereotyped behaviour, Compulsive behaviour, Restricted preferences, Repetitive use of language, Insistence on sameness. Repetitive use of language and restricted preferences subscales cannot be scored for individuals with no language because two of the three items in the subscale require the person to be verbal. The frequency of each behaviour is scored on a 5-point Likert scale (0-4). Two scoring systems can be applied for verbal (total score range from 0-76) and non-verbal individuals (total score range from 0-60). Items that are dependent on the person being verbal can be excluded when comparing verbal and non-verbal individuals. Clinical cut-offs for each subscale are reached if the individual scores three or more on at least 1 item (behaviours occurs 'once a day' or 'more than once a day'). The scale has good psychometric properties with inter-rater reliability ranging from 0.46 to 0.80, test-retest reliability ranging from 0.61 to 0.93 and good internal consistency for the total scale, stereotypies and compulsive subscale (Cronbach's alpha = >0.80, >0.70 respectively). Alpha levels for the Repetitive use of language, Restricted preferences and Insistence on sameness were 0.54, 0.50 and 0.64. Concurrent validity, established with the Repetitive Behaviour subscale of the Autism Screening Questionnaire, was good (0.60) (Moss et al. 2009).

#### *5.5.1.10 Developmental Behavior Checklist (DBC)*

The DBC (Einfield and Tonge 1995) is an informant-based questionnaire reporting behavioural and emotional problems over a 6 months period (i.e. appears depressed, downcast or unhappy, avoids eye contact, won't look you straight in the eye). The DBC-Primary Carer Version contains 96 items and assesses behavioural problems in young people aged 4-18 years; the DBC-Adult contains 106 items and assesses behavioural problems in the adult population with ID. Behavioural problems are rated on a 0 to 2 scale, where 0 = not true; 1 = sometimes/somewhat true; 2 = often true. Both

versions have high internal consistency and inter-rater reliability (DBC-P Inter-rater reliability = 0.80, internal consistency = 0.94; DBC-A inter-rater reliability = 0.72, internal consistency = 0.95). The DBC contains an Autism Screening Algorithm, which is a 29 item scale designed to discriminate children (<18 years) with autism and ID from others with ID (internal consistency is = 0.94) (Brereton et al. 2002).

#### *5.5.1.11 Vineland Adaptive Behavior Scale – Survey Form (VABS, Sparrow et al. 1984)*

The VABS (Sparrow et al. 1984) survey form contains 297 items, which assess adaptive behaviour in children and adults with and without intellectual disabilities. The scale is divided into four domains: Communication, Daily Living Skills, Socialization and Motor Skills. A group of 3,000 individuals from birth to 18 years of age were used as national standardization sample. Standard scores (mean = 100; SD= 15) and age equivalent scores can be combined to derive an Adaptive Behavior Composite. Internal consistency (median Communication 0.89, Daily Living skills 0.90, Socialization 0.86, Motor skills 0.83, Adaptive Behavior Composite 0.94) and test re-test reliability (Communication 0.86, Daily Living Skills 0.85, Socialization 0.81, Motor Skills 0.81, Adaptive Behavior Composite 0.88) of the Survey form is good and inter rater reliability is adequate (Communication 0.75, Daily Living skills 0.72, Socialization 0.62, Motor skills 0.78, Adaptive Behavior Composite 0.74) (Sparrow et al. 1984), confirmed by several other studies exploring adaptive skills in the ASD and ID populations (DeBildt et al. 2005; Perry and Factor 1989).

### ***5.5.2 Family Measures***

The second booklet contained measures that assess family health, mental health, positive perception, level of support received from the family and agencies, parental perception of progression/regression of behavioural and clinical symptoms and the experience of siblings.

#### *5.5.2.1 Background information*

Questions asked for demographic information about the parents, their levels of education, marital status, numbers of children and adults in the family, living accommodation of the person with RTT and information about the relationship of the partner with the person with RTT.

#### *5.5.2.2 Questionnaire on Resources and Stress-short form (QRS-S)*

The QRS (Friedrich, Greenberg and Crnic 1983) was originally developed as a 285 item scale to assess the impact that a developmental disability or critical illness has on family members. It measures positive and negative impacts that the child has on adaptation and coping strategies adopted by the family. There is no report on the internal reliability of the original scale which has been used with only a small sample, thus precluding factor analysis. A shorter scale with established psychometric properties was developed to measure stress in families with a child/adult with developmental disability. The QRS – short form consists of 52 items divided into four factors: parent and family problems (20 items), pessimism (11 items), child characteristics (15 items) and physical incapacity (6 items). The purpose of this study was to analyse family stress in relation to clinical and behavioural problems of the child, thus only 15 items of the Parents and Family Problems (the 5 items that seem to measure depression were

excluded) were included in the questionnaire (i.e. other members of the family have to do without things because of, our family agrees on important matters).

#### *5.5.2.3 Positive Gain Scale (PGS)*

The PGS (Pit-ten Cate 2003) was designed to measure positive outcomes of parents from raising a child with ID (i.e. since having this child I feel I have grown as a person, having this child has helped me to learn new things/skills). The scale consists of seven items rated on a 5 point Likert scale from 1 (strongly agree) to 5 (strongly disagree) lower scores indicating greater positive gains: 5 items describe perceived positive experience from raising a child with ID and 2 positive experiences gained by the family as a whole. Two other studies have used the PGS and both have found good internal consistency (Conbrach's  $\alpha = 0.87$ ; Weiss and Lunskey 2010; Conbrach's  $\alpha = 0.80$ ; McDonald et al. 2010).

#### *5.5.2.4 Hospital Anxiety and Depression Scale (HADS)*

The HADS (Zigmond and Snaith 1983) is a self-assessment scale that measures anxiety and depression (i.e. I feel tense or "wound up", I still enjoy the things I used to enjoy). The scale was first developed for use in an outpatient clinic setting, but has been widely used with parents of children with ID. The scale consists of 14 items, 7 measuring anxiety and 7 depression, both with a score ranging from 0 to 21. A score above 11 in the depression and anxiety subscales indicates an abnormal level of anxiety and depression. The scale shows good psychometric properties and it has been demonstrated that it is a valid scale for assessing severity of anxiety and depression disorder. Internal consistency has been found to be good for both HAD- A (Cronbach's  $\alpha = 0.78-0.98$ ) and HAD-D (Cronbach's  $\alpha = 0.82-0.90$ ) (Mykletuna et al. 2001).

#### *5.5.2.5 Positive Affect Scale*

The items for the Positive Affect scale were derived from the Positive and Negative Affect scale (PANAS; Watson et al. 1988). The scale comprises 10 items describing positive affect (i.e. interested, strong, excited). Families were asked to rate the ten items on a 5 points scale (1 = very slightly or not at all, 2 = a little, 3 = moderately, 4 = quite a bit, 5 = extremely). The scale has good psychometric properties, with high internal consistency (Cronbach's alpha ranging from 0.86 to 0.90) and test re-test reliability (ranging from 0.47 to 0.68) (Watson et al. 1988).

#### *5.5.2.7 Parental Perception of Regression or Progression*

A series of questions were designed specifically for this study to investigate parental perception of progression and/or regression over the past 3 years in behavioural and clinical symptoms associated with RTT (whether symptoms were getting better = 1, staying the same = 0 or getting worse = -1). Questions were based on the 8 domain areas of the RSBQ (Mount et al. 2002b): breathing abnormalities, physical fitness and robustness, mobility and walking, communication, purposeful hand use, repetitive hand movements, body rocking, mood changes, anxiety, sleep and feeding/nutrition. An overall indicator of parental perception of regression/progression of skills were calculated by summing scores of the 8 domains. In some cases parents indicated that there was no problems in one or more domains, thus a score of 2 = not a problem was decided to be assigned to the item. Higher score indicates a perception of progression of skills, scores near 0 indicates a perception of stagnation of skills and a negative score indicates a perception of regression/deterioration of skills.

## 5.6 Data analysis

### 5.6.1 Missing data

For a few participants, some items of the two questionnaires were not completed. Guidelines from questionnaire manuals were employed for pro-rating missing data for the AQ, RSBQ, DBC, MIPQ, RBQ, QRS and HADS.

In order to minimize missing data, the following was done:

- Ask parents to answer the missing questions where possible during the telephone interview undertaken to complete the VABS.
- Complete the item in question from information provided in response to another question.
- Substitute the mean for the subscale for measure with subscales, providing that:
  - 75% of items are scored for the MIPQ and AQ
  - 65% of items in each subscale are rated for the RBQ
  - 90% of items are rated in the DBC, RSBQ, QRS and HADS

Having done this, 2 cases were excluded from analysis of the MIPQ and DBC due to missing data, 1 participant was excluded from analysis of the AQ, RSBQ and QRS. The same case was excluded from analysis of the RSBQ and QRS.

### 5.6.2 Normality tests

Data were tested for normality using the Kolmogorov-Smirnov test and a critical region of  $p < .05$ . Results from such testing and examination of skewness and kurtosis revealed that data on diagnostic classification, age groups, mutation group, age of regression, total severity score and severity domains were non-normal. Non-parametric

tests were used to explore differences between groups in these cases (see *Appendix D – 1: Normality tests*).

### 5.6.3 Analysis

The survey was designed to investigate the following aspects of RTT:

- Description of behavioural characteristics of RTT.
- Behavioural changes across age groups, ages of regression, diagnostic categories and mutation types.
- Differences in behavioural characteristics within subjects and across groups with rare genetic syndromes.
- The impact that severity of behavioural and clinical presentation have on family stress and mental health.

Subsequent analysis was divided into three parts. Part One explored the physical phenotype of RTT and abilities of the sample. Analysis focused on comparison of regression features, the health and physical phenotype (using the Health Questionnaire), clinical severity score in relation to age, mutation (whether a mutation in the *MECP2* gene had been identified and, if so, the nature of the mutation) and diagnostic classification (Classic, Atypical and *MECP2* related disorder).

Part Two explored behavioural phenotypic features of the RTT group. Data were analysed to provide a description of behavioural and emotional characteristics of RTT, behavioural differences across age, diagnostic and mutation groups within RTT and behavioural differences between participants with RTT and those with other rare genetic syndromes (see paragraph 5.4 for matched control group).

Part Three explored the impact that severity of behavioural and clinical presentations have on family stress and mental health. In addition positive aspects of having a child with a disability were investigated.

Total and subscale mean scores for the AQ, MIPQ, RSBQ, RBQ and DBC were calculated and analysed in relation to age, and severity of clinical phenotype. Within group behavioural differences were explored by analysing specific behavioural features (RSBQ, DBC) in relation to age groups, diagnostic categories and types of mutation. The DBC-Autism Algorithm was used to investigate autistic feature in the RTT sample.

Differences/similarities between the RTT and Control groups were addressed by comparing overactivity and hyperactivity (AQ), mood and interest (MIPQ), and self-injurious and repetitive behaviour (RSB).

## CHAPTER 6

### CLINICAL CHARACTERISTICS AND DESCRIPTION OF THE SAMPLE

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#### 6.1 Introduction

The following chapter presents descriptive and clinical data on the survey participants. These include demographic characteristics of the individuals with RTT and their families, clinical characteristics of the individuals with RTT and severity of the clinical phenotype, the nature of their regression, typical RTT features, current abilities, epilepsy status and health problems. Total sample size included 91 females with a diagnosis of RTT. Eighty-nine percents (80) lived at home and 12.1% (11) lived in residential/supported living accommodation.

#### 6.2 RTT sample characteristics

The ages of the RTT sample ranged from 4 to 47 years with a mean of 20.5 years. All participants with RTT were female. The majority (87.9%) lived in the family home. The remainder lived in residential homes, supported living or other accommodation not specified. Sixty-nine had classic RTT (75.8%), 19 atypical RTT (20.9%) and 3 a *MECP2*-related disorder (4.3%). Seventy-one are known to be *MECP2* positive (78%). Diagnosis of RTT was made by a pediatrician in 42.9% of cases, a clinical geneticist in 26.4%, by both a pediatrician and clinical geneticist in 3.3% and by another professional in 25.3% (this information was missing in 2.2% of the cases). Median age of diagnosis was 3.0 years (range, 1-39 years). Diagnosis occurred most commonly between 2 and 4 years of age. Mean age of regression was 18.9 months (range, 6-84 months; SD 11.75).

The RTT sample was divided into 4 age groups: <12 years (childhood: n=20, 22.0%), 12-17 years old (adolescence: n=23, 25.3%), 18-25 years (early adulthood: n=21, 23.1%) and 26+ years (adulthood: 27, 29.7%) and into 3 diagnostic categories according to the Neul et al. (2010) criteria: Classic (n=69, 75.8%), Atypical RTT (n=19, 20.9%) and *MECP2*-related disorder (n=3, 3.3%)<sup>2</sup>. Seventy-one of the total sample (78%) had a confirmed *MECP2* mutation: 52 in the Classic group (75.4%) and 16 in the Atypical group (84.2%) in addition to the three with *MECP2*-related disorder. In addition, the sample was divided into 6 groups based on presence/absence of a *MECP2* mutation and the location of that mutation<sup>3</sup>: Missense (n=23, 25.3%), Early Truncating (n=26, 28.6%), Late Truncating (7, 7.7%), C-Terminal (13, 14.3%), Large Deletion (2, 2.2%) and no Mutation (n=20, 22.0%). Subgroups were also created according to the abilities to walk (able to walk: n=47, 51.6%; unable to walk: 44, 48.4%) and speak or sign more than 30 words (able to do so: n=3, 3.3%; not able to do so: n=88, 96.7%). See *Appendix E – 1: Most common mutation* and *Appendix E – 3: Type and location of mutations in the RTT sample* for frequency of the single mutations and mutations included in each subgroup.

### 6.3 Family demographic characteristics

Tables 6.1 summarises the demographic characteristics of the families. Mean ages of mothers and fathers were 50.9 and 53.9 years respectively. The majority of the mothers (or fathers) were married or living with a partner. In 62 cases (68.1%), the partner was the biological father (or mother) of the child with RTT. The educational status of mothers and fathers varied from no formal qualifications to post-graduate

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<sup>2</sup> Although participants were recruited using the Hagberg et al. (2002) Diagnostic Criteria, analysis will focus on exploring differences and similarities in relation to the newly revised diagnostic categories.

<sup>3</sup> Although data on the precise location of the *MECP2* mutation were available, broad categories were created to avoid subgroups being too small to analyse.

level, with each category of educational level represented. The range in family incomes was also wide and fairly evenly distributed across the sample.

**Table 6.1 Family demographic characteristics**

Mean maternal age in years (range, SD)		50.89 (30-71, 9.25)
Mean paternal age in years (range, SD)		53.87 (30-78, 10.08)
Marital status	Married	68 (74.7%)
	Living with partner	8 (8.8%)
	Divorced/widow/single	15 (16.5%)
Maternal education	No formal qualification	8 (8.8%)
	Fewer than 5 GCSE	13 (14.3%)
	5 or more GCSE, NVQ	26 (28.6%)
	NVQ3, A level	8 (8.8%)
	University degree, NVQ4	29 (30.8%)
	Master/Doctoral degree/NVQ5	5 (5.5%)
Paternal education	No formal qualification	15 (16.5%)
	Fewer than 5 GCSE	15 (16.5%)
	5 or more GCSE, NVQ	7 (7.7%)
	NVQ3, A level	9 (9.9%)
	University degree, NVQ4	22 (24.2%)
	Master/Doctoral degree/NVQ5	8 (8.8%)
Income	< £15,000	12 (13.2%)
	£15,001-£25,000	25 (27.5%)
	£25,001-£35,000	10 (11.0%)
	£35,001-£45,000	11 (12.1%)
	£45,001-£55,000	6 (6.6%)
	£55,001-£65,000	5 (5.5%)
	>£65,000	14 (15.4%)

#### 6.4 Clinical characteristics of the RTT sample

This section will explore data regarding clinical development of the child (mother's pregnancy, delivery, early development, head circumference, slowing of head growth).

One of the necessary criteria for RTT in the Hagberg et al. (2002) diagnostic criteria included an apparent normal prenatal, perinatal and postnatal development, although normal early development is not necessary in the new diagnostic criteria (Neul et al. 2010). Eight-five (93.4%) of mothers experienced a normal pregnancy and 74 (81.3%) a normal delivery. The majority reported normal development in the first few months of life (85.7%) with no apparent problems (73.6%). Head circumference at birth was normal (81.3%), although slowing of head growth occurred among 34 individuals (37.4%).

The RTT participants' clinical characteristics were tested in relation to diagnostic groups and types of mutation. There were no significant differences between diagnostic categories or types of mutation for pregnancy ( $\chi^2_{(2)} = .520, p > .05$ ;  $\chi^2_{(5)} = 2.368, p > .05$ ), delivery ( $\chi^2_{(2)} = .752, p > .05$ ;  $\chi^2_{(5)} = 1.028, p > .05$ ), problems in the first months ( $\chi^2_{(2)} = 1.280, p > .05$ ;  $\chi^2_{(5)} = 3.205, p > .05$ ), or early development ( $\chi^2_{(2)} = .260, p > .05$ ;  $\chi^2_{(5)} = 13.255, p < .05$ ). However, there was a significant difference in slowing of head growth after birth between types of mutation ( $\chi^2_{(5)} = 12.034, p < .05$ ). Cases with missense mutation were more likely to have had a slowing of head growth compared to those with no mutation ( $U = 63.5, z = -2.463, p < .05$ ), or early truncating mutation ( $U = 95.0, z = -2.582, p < .05$ ).

## 6.5 Regression features

Regression was reported in 87 (95.6%) of the sample. In one case (1.1%), the mother was not sure if the child had had a regression and, in 3 others (3.3%), they reported that the child did not have a regression. The most common month for regression was 18 months (18.7% of cases). Overall, 15 (16.5%) had a regression before 12 months, 49 (53.8%) between 12 and 18 months, 18 (19.0%) between 19 and 36 months and 5 (5.5%) after 36 months (including, 1 participant who had a late regression at 7 years). Data on regression are summarised in Table 6.2 which also shows the information separately for each diagnostic group. Individuals in the *MECP2*-related disorder did not have regression<sup>4</sup>, thus only a difference in age of regression between Classic and Atypical cases is explored. A Mann-Whitney U test revealed no significant differences between the classic and atypical group ( $U = 530.5$ ,  $z = -.953$ ,  $p > .05$ ). Moreover, there was no significant difference in age of regression between mutation groups ( $\chi^2_{(5)} = 5.736$ ,  $p > .05$ ).

**Table 6.2 Age of regression in relation to diagnostic group (Neul et al. 2010)**

	<12 months (15)	12-18 month (49)	19-36 months (18)	>36 months (5)	No regression (4)
Classic	11 (15.9%)	39 (56.5%)	15 (21.7%)	4 (5.7%)	0
Atypical	4 (21.1%)	10 (52.6%)	3 (15.8%)	1 (5.3%)**	1 (5.3%)*
<i>MECP2</i> -related disorder	0	0	0	0	3 <sup>#</sup> (100%)

\* In 1 subject the mother was not sure if the girl had regression. Another girl fulfills 3 of 4 main criteria, not enough for a diagnosis of RTT.

# Parents reported no progression rather than regression in skills. This was reported by 9 months.

\*\*She had later than usual regression in hand use. Lost the ability to finger feed at 4 yr. She did not have regression in speech. No words reported until 4 yr. She could use few words at 10 yr.

Loss of previously acquired skills was reported in over 90% of the sample. Loss of hand use was reported in 92.3% of the sample, loss of communication skills in 83.7%,

<sup>4</sup> RTT is a clinical diagnosis supported by genetic testings. A history of regression of previously acquired skills is important and a diagnosis of RTT cannot be given in the absence of a regression stage.

loss of mobility in 70.3% and loss of social contact in 53.8%. In one case, the parent reported that the child had never gained any skills in communication, mobility, functional hand use and sociability<sup>5</sup>. There was no significant difference in loss of previously acquired skills between diagnostic categories.

## 6.6 Current abilities

According to parental report, 14 individuals (15.4%) had retained some words/speech, although only 3 (3.3%) of the sample had 30 or more words. About two-thirds could communicate with gesture or sound (predominantly with eye contact or eye pointing) and make a choice between two items (65.9% and 67.0%, respectively). Although hand use was lost during regression in most girls, small percentages could still feed with fingers and/or use a spoon or fork (36.9% and 17.6%, respectively). The abilities to reach for an object and hold an object were retained (or regained in some of the cases) in 52.7% and 35.2%. Although the ability to walk was impaired, over half of the sample could walk with support (N = 48, 52.7%) and 34 (37.4%) were able to walk independently. No significant differences in current abilities were found between the diagnostic groups except in relation to speaking ( $\chi^2 (2) = 9.158, p < .05$ ). The 3 girls diagnosed with *MECP2*-related disorder were more likely to speak. In fact all 3 participants were reported to be able to use 30 or more words.

Table 6.3 presents participants' abilities across age groups. A Kruskal-Wallis test revealed no significant differences between the age groups except for the abilities to make choices ( $\chi^2 (3) = 12.793, p < .05$ ) and reach for objects ( $\chi^2 (3) = 8.425, p < .05$ ). *Post-hoc* (critical level of significance corrected  $p < .001$ ) analysis revealed that adults (26

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<sup>5</sup> In this case, the mother reported that she did not develop skills in all 4 areas (communication, mobility, hand skills and sociability), however a check with the BIRSS indicated that the girl did not develop any speech or babble, hence the diagnosis of Atypical RTT.

years+) were less likely to make choices compared to children (<12 years,  $U = 175.0$   $z = -2.379$ ,  $p < .05$ ) and young adults ( $U = 161.0$   $z = -2.652$ ,  $p < .05$ ) and children were more likely to reach for objects compared to those aged 18-25 years ( $U = 122.0$   $z = -2.689$ ,  $p < .05$ ) and 26 years+ ( $U = 174.0$   $z = -2.430$ ,  $p < .05$ ).

**Table 6.3 Current abilities in relation to age groups**

	>12 yrs (n=20)	12-17 yrs (n=23)	18-25 yrs (n=22)	26+ yrs (n=27)
Concentrate	18 (90.0%)	20 (87.0%)	19 (90.5%)	22 (81.5%)
Hold objects	7 (35.0%)	7 (30.4%)	7 (33.3%)	11 (40.7%)
Reach for objects	16 (80.0%)	12 (52.2%)	8 (40.9%)	12 (44.4%)
Sit unsupported	15 (75.0%)	11 (47.8%)	15 (71.4%)	15 (55.6%)
Walk with support	7 (35.0%)	10 (43.5%)	14 (66.7%)	17 (63.0%)
Walk unsupported	4 (20.0%)	7 (30.4%)	12 (57.1%)	11 (40.7%)
Feed with finger	5 (25.0%)	9 (39.1%)	8 (38.1%)	11 (40.7%)
Feed with fork/spoon	1 (5.0%)	3 (13.0%)	6 (28.6%)	6 (22.2%)
Communicate with gesture or sounds	16 (80.0%)	16 (69.6%)	13 (61.9%)	15 (55.6%)
Speak words*	1 (5.0%)	3 (13.0%)	6 (28.6%)	4 (14.8%)
Make choices	18 (90.0%)	16 (69.6%)	16 (76.2%)	11 (40.7%)

*Percentages vary due to missing data.*

\* Only 3 participants had more than 30 words or signs

## 6.7 Characteristic features of RTT

Loss of functional hand skills, followed almost immediately by the appearance of hand stereotypies such as hand wringing, clapping and tapping, was reported in almost all cases. Other features associated with RTT include breathing abnormalities, such as breath holding and hyperventilation, teeth grinding and sleep disturbances. Inspection of Table 6.4 indicated that characteristic features of RTT were reported in the vast majority of the sample with hand stereotypies being present in almost all and breathing

abnormalities, such as breath holding and hyperventilation present in nearly three-quarters of the sample. Rett ‘episodes’ (a non-epileptic behaviour often identified as a possible seizure in which the eye gaze is not fixed, the person appears not to be breathing, with absence of hand movements and motor activities) were also frequent (72.6%). Parents were asked to indicate the cause of these episodes. The majority were either not sure of the cause or reported that they might be related to seizures. There was a significant difference between diagnostic categories in breath holding ( $\chi^2_{(2)}=8.379, p<.05$ ) Individuals with Classic RTT were more likely to present with breath holding compared to those with Atypical and *MECP2*-related disorders. Other physical features also reported included hypotonia, small hands and feet and scoliosis.

**Table 6.4 Characteristic RTT features in relation to age**

	<12 yrs (20)	12-17 yrs (23)	18-25 yrs (22)	26+ yrs (27)	Total (91)
Hand stereotypies	20 (100%)	22 (95.7%)	21 (100%)	27 (100%)	90 (98.9%)
Teeth grinding	14 (70.0%)	14 (60.9%)	11 (52.4%)	13 (48.1%)	52 (57.1%)
Breath holding	16 (80.0%)	19 (82.6%)	18 (82.6%)	17 (63.0%)	70 (76.9%)
Hyperventilation	12 (60.0%)	13 (56.5%)	11 (52.4%)	17 (63.0%)	53 (58.2%)
Sleep difficulties	12 (60.0%)	15 (65.2%)	10 (42.6%)	19 (70.4%)	56 (61.5%)
Daytime sleep	4 (20.0%)	8 (34.8%)	9 (42.9%)	12 (44.4%)	33 (36.3)
Rett ‘episodes’	16 (80.0%)	16 (69.6%)	16 (76.2%)	18 (66.7%)	66 (72.5%)

Table 6.4 presents the distribution of RTT features in relation to age. There were no significant differences. Although not at a statistically significant level, children aged under 12 years (35.0%) and between 12 and 17 years (30.4%) were more likely to present with constant breathing abnormalities compared to the adult groups (18-25 years

19.0%, 26 years+ 14.4%). Sleep difficulties were more present in the adult group (26 years+) and daytime sleep increased with age.

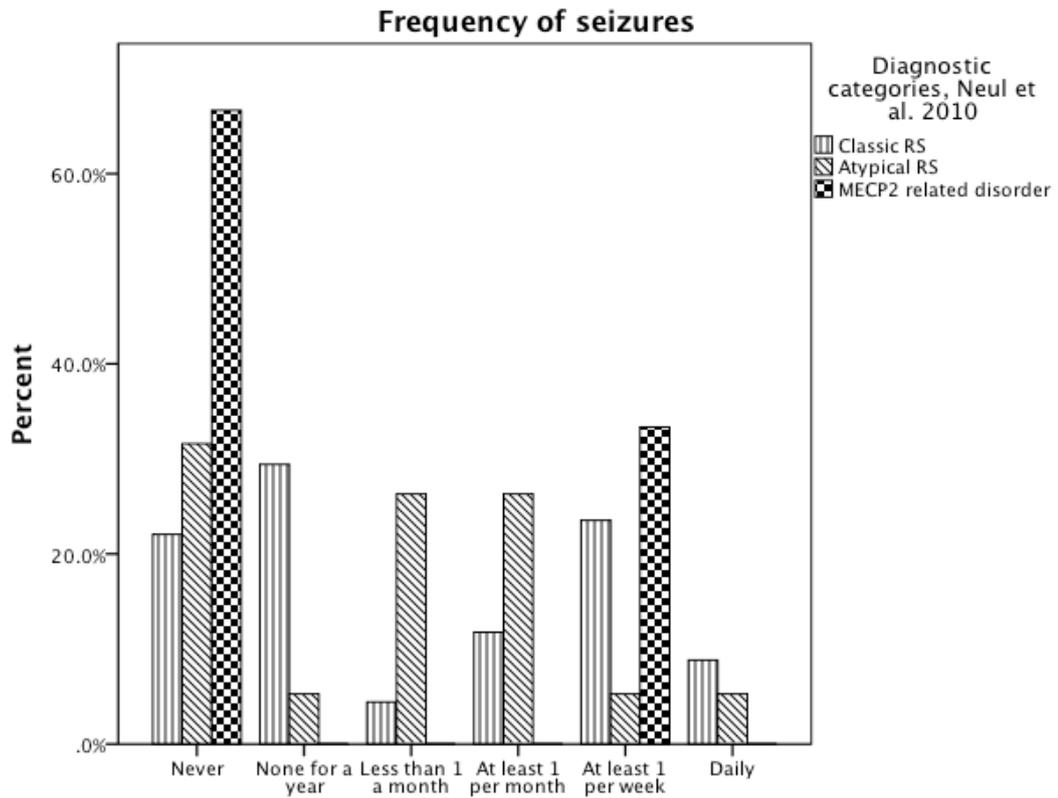
## 6.8 Epilepsy

Over half of the sample were reported to have epilepsy and to be currently on anti-epilepsy medication (see Table 6.5). Age of onset of seizures ranged from 0 to 18 years (mean age 5.8 years, SD 4.19), although the mother indicated in one case that seizures started before the girl was born. Figure 6.1 shows reported frequency of seizures. A substantial proportion had not experienced seizures for many years, indicating that their fits were well controlled by medication or did not occur. In contrast, a quarter of the sample were reported to have seizures daily (7.7%) or weekly (19.8%).

**Table 6.5 Distribution of individuals that currently have epilepsy, experienced epilepsy in the past and medication across age groups.**

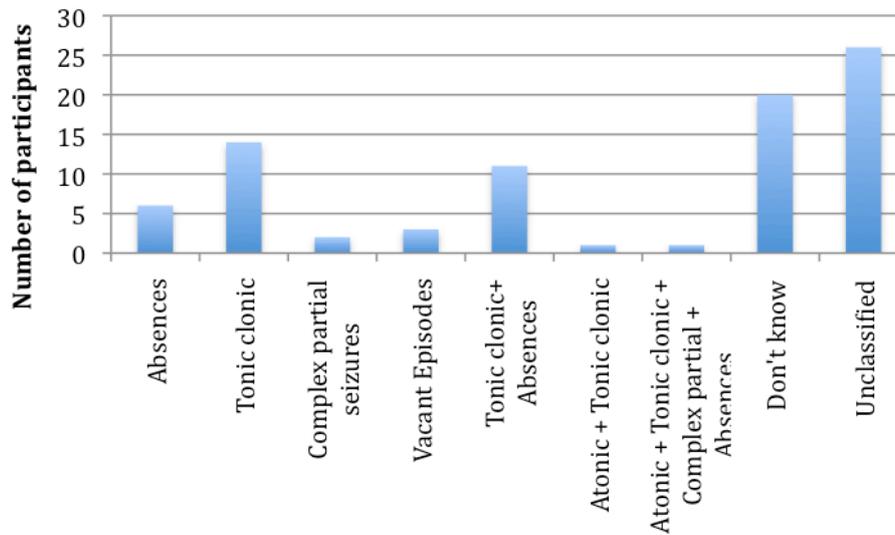
	>12 yrs (n=20)	12-17 yrs (n=23)	18-25 yrs (n=21)	26+ yrs (n=27)	Total
Currently has fits	16 (80.0%)	17 (73.9%)	13 (61.9%)	10 (63%)	63 (69.2%)
Used to have fits	0	1 (4.3%)	1 (4.5%)	3 (11.1%)	5 (5.5%)
Medication	14 (70.0%)	15 (65.2%)	12 (57.1%)	18 (66.7%)	59 (64.8%)

**Figure 6.1 Frequency of seizures (%)**



A higher percentage of people with Classic RTT were reported to experience weekly or daily seizures (23.2% and 10.1% respectively) compared to those with Atypical RTT and *MECP2*-related disorder (both 5.6%). Twenty-three percent (n = 20) of the parents did not know the type of the seizure and 30.6% (n = 26) were not able to specify the type of seizure their child had. The variety of seizure types among the remainder is shown in Figure 6.2.

**Figure 6.2 Type of fits (N)**



### 6.9 Health problems in the Rett phenotype

The heights and weights of the sample ranged from 1.00 m to 1.78 m (mean 1.42 m; SD 0.16) and from 12.25 kg to 85.00 kg (mean 39.58 kg; SD 13.97) respectively. Body Mass Indices (BMI: weight divided by height squared) ranged from 12.11 to 32.99 (mean 19.61; SD 4.63). The highest proportion of the sample<sup>6</sup> (43.1%) had a BMI < 18.5 (mean 15.4, SD 19.3) and were thus considered to be underweight; closely followed by 41.7% who had normal weight (mean 21.0%, SD 14.5). 13.9% and 1.1% respectively had BMI scores between 25 and 29.9 (overweight) and 30 or above (obese). Those overweight or obese were individuals with a less severe phenotype (severity scores 4 - 6).

Table 6.6 lists the percentage occurrence of a variety of health problems ever in the past and in the last month. Mean Overall Health score in the previous month was 3.35 (SD 3.30) and during the person's life 9.49 (SD 5.82). The most common ever in the

<sup>6</sup> A BMI under 18.5 is considered underweight, a BMI between 18.5 and 24.9 is considered normal weight, a BMI between 25 and 29.9 is considered overweight and a BMI equal to or greater than 30 is considered obese. Data were available on 72 subjects.

past were epilepsy (79.1%), gastrointestinal problems (60.4%), bowel problems (56.0%), dental problems (42.8%) and skin problems (40.6%). Medication for epilepsy and the relatively good control of fits is described above. The most common health problem in the last month was also epilepsy (51.6%). High or moderate proportions were also reported for bowel (41.7%), gastrointestinal (35.1%), skin (29.7%) and lung/respiratory (11.0%) problems. There were no significant differences in the distribution of health problems between diagnostic groups.

**Table 6.6 Distribution of health problems during the person’s life and in the last month**

	Ever	In the last month
Ear problem	33 (36.3%)	5 (5.5%)
Eye problem	20 (22.0%)	8 (8.8%)
Dental problem	39 (42.8%)	11 (12.1%)
Cleft palate	2 (2.2%)	1 (1.1%)
Gastrointestinal problem	55 (60.4%)	33 (36.3%)
Bowel problem	51 (56.0%)	38 (41.7%)
Heart problem	9 (9.9%)	5 (5.5%)
Hernia	4 (4.4%)	2 (2.2%)
Limb abnormalities	9 (9.9%)	6 (6.3%)
Epilepsy/seizure	72 (79.1%)	47 (51.6%)
Lung/respiratory	26 (28.6%)	10 (11.0%)
Liver/kidney	3 (3.3%)	2 (2.2%)
Diabetics/ thyroid	1 (1.1%)	2 (2.2%)
Skin problem	37 (40.6%)	27 (29.7%)

Comparison of the overall health score between diagnostic groups revealed a significant difference ( $\chi^2 (2) = 9.972, p < .05$ ) in the overall health score in the person’s

life. Post-hoc analysis indicated that individuals diagnosed with Classic RTT experienced greater health problems during their life compared to individuals diagnosed with atypical RTT ( $U = 351.0$   $z = -3.096$ ,  $p < .005$ ). No significant differences across age groups were identified.

## **6.10 Severity of the clinical phenotype**

A simplified Severity Score was used in this study (see section 5.5.1.3 for description of the measure). Total Severity Scores ranged from 3 to 15 (mean 8.6, SD 3.16). Distributions of severity in each domain are presented in *Appendix E-3 – E-9: Total and domain severity scores*. Fifty-one (56.0%) retained the ability to sit independently and 35.2% (32) had lost the ability (in 1 participant the ability to sit was never gained and in further 7 the skill was reported to be impaired). 44.9% could still walk but their ability was impaired due to the impaired gait typical of RTT, 15.4% had lost the ability to walk and 33.0% had never learned to walk. Hand use was either lost (57.1%) or reduced (37.4%) or never acquired (5.5%). Verbal ability was lost or never acquired in the vast majority (61.5% and 23.1% respectively). Epilepsy was diagnosed in 67.0% of the sample, though controlled by medication. The majority of the sample had some degree of scoliosis (59.4%, requiring surgery in 29.7%).

### *6.10.1 Severity of clinical symptoms in relation to age groups*

Total and domain severity scores were compared across the four age groups. Table 6.7 shows total severity scores by age group, together with the percentages of individuals presenting with a mild phenotype (score  $\leq 9$ ) or more severe phenotype (score  $>9$ ). Although the adolescent group (12 to 17 years old) had a slightly higher

mean total severity score, analysis did not reveal a significant difference between the age groups ( $\chi^2_{(3)} = 1.980$ ,  $p > .05$ ).

**Table 6.7 Mean Total Severity Scores (range) and percentages of individuals presenting a mild or severe phenotype in the four age groups**

Domains	<12 yrs (n=20)	12-17 yrs (n=23)	18-25 yrs (n=22)	26+ yrs (n=27)
Total Score	8.4 (4 – 14)	9.2 (3 – 14)	7.9 (3 – 14)	8.7 (4 – 15)
Mild (N=55)	75.0%	47.8%	61.9%	59.3%
Severe (N=36)	25.0%	52.2%	38.1%	40.7%

#### 6.10.2 Severity of clinical presentation in relation to MECP2 mutation groups

Total and domain severity scores were analysed across mutation groups. Inspection of Table 6.8 indicates that individuals with a Late Truncating mutation had a lower mean severity score compared to the other groups. Kruskal-Wallis analysis of variance revealed significant differences between the mutation groups in the total severity score ( $\chi^2_{(5)} = 11.620$ ,  $p < .05$ ) and in the walking domain ( $\chi^2_{(3)} = 16.317$ ,  $p < .05$ ). *Post Hoc* (Mann-Whitney test critical level of significance correct,  $p < .01$ ) analysis confirmed that individuals with a Late Truncating mutation had a lower total severity score compared to those with no mutation ( $U = 1.250$ ,  $z = -2.507$ ,  $p < .05$ ) and an Early Truncating mutation ( $U = 22.5$ ,  $z = -3.038$ ,  $p < .005$ ) in the total severity score. Cases with a Late truncating mutation had a lower score in the walking domain compared to those with Early Truncating ( $U = 28.5$ ,  $z = -2.955$ ,  $p < .005$ ). Analysis of the most common mutations indicated that there were no significant differences in severity score ( $\chi^2_{(9)} = 14.279$ ,  $p > .05$ ). R294X was the mutation associated with the lowest severity score. Milder mutations also included the R168X, R270X and C-Terminal mutations. In

contrast with other studies, the R133C mutation was associated with a severe clinical phenotype.

**Table 6.8 Mean Total Severity Score (SD, range) in relation to mutation groups**

	No mutation (n=20)	Missense (n=23)	Large Deletion (n=2)	C-Terminal (n=13)	Late Truncating (n=7)	Early Truncating (n=26)
Mean Severity Score (SD, range)	9.05 (3.34, 4-15)	8.13 (3.09, 4-15)	9.5 (2.12, 8-11)	8.07 (3.20, 3-14)	5.42 (2.37, 3-10)	9.69 (2.89, 4-14)

### 6.10.3 Severity score in relation to age of regression

Inspection of Table 6.9 indicates that individuals with a regression age between 19 and 36 months had a lower mean severity score compared to the other groups. Kruskal-Wallis analysis of variance revealed a significant difference in the walking domain ( $\chi^2_{(3)} = 16.262, p < .005$ ) and in the total severity of the clinical phenotype ( $\chi^2_{(3)} = 10.086, p < .05$ ). Results of *Post Hoc* (Mann Whitney test critical level of significance correct at  $p < .01$ ) analysis confirmed that individuals that had regression before 12 months presented a more severe phenotype (total severity score) and were less likely to be able to walk compared to those with a regression age between 19 and 36 months ( $U = 44.5, z = -3.294, p < .005$ ;  $U = 31.5, z = 3.989, p < .001$ ).

**Table 6.9 Mean Total Severity Score (SD, range) in relation to age of regression**

	No regression (n=4)	< 12 months (n=15)	12-18 months (n=49)	19-36 months (n=18)	>36 months (n=5)
Total Severity Score (SD, range)	8.75 (5.18, 4-15)	10.26 (2.40, 5-15)	8.66 (3.12, 3-14)	6.88 (2.51, 3-12)	9.20 (3.89, 5-13)

## 6.11 Discussion

This chapter presented descriptive and clinical data on 91 cases with RTT.

Nearly 80% of the sample had a positive mutation in the *MECP2* gene. Not all individuals in the sample had been tested, but only 1 case diagnosed with Classic RTT was confirmed not to have a mutation in the *MECP2* gene. This finding is consistent with the literature that a mutation in the *MECP2* gene can be found in over 90% of cases with Classic RTT (Neul et al. 2010).

Pregnancy and birth were reported to be normal in the great majority and high proportions appeared to develop normally in the first few months with no apparent problems. Although there is now evidence of subtle developmental problems in the first few months (Burford et al. 2003; Einspieler et al. 2005; Leonard and Bower 1997; Witt-Engerstrom 1987), apparent normal development in the first few months is reported by most parents and it is now recommended that an atypical diagnosis be considered if abnormal development is noticed (Neul et al. 2010).

Regression of previously acquired skills, such as hand skills, communication and mobility is one of the characteristic features of RTT and was reported by nearly all of families. Consistent with other studies, the most common age of regression was between 12 and 18 months. Individuals diagnosed with Classic RTT were more likely to have had a regression before the age of 12 months, to have lost functional hand use and language abilities and to have breathing abnormalities, such as hyperventilation and breath holding compared to individuals diagnosed with Atypical RTT and *MECP2*-related disorder. The latter group was reported to be more able to speak than the other two groups. Clinical and characteristic features of the syndrome were also tested in relation to age groups. Although features such as breathing abnormalities, vacant spells, teeth grinding and sleep difficulties were reported most often in the younger groups,

analysis did not reveal significant differences between the age groups. Age of regression appeared to predict level of severity. In fact, individuals with an age of regression before 12 months were less likely to be able to walk and to have higher total severity scores compared to those with an age of regression between 19 and 36 months.

Health problems most commonly reported included epilepsy, scoliosis, gastrointestinal, bowel and dental problems. Participants diagnosed with the classic form of the syndrome had a higher Overall health score compared to individuals with Atypical RTT. Generally, adults ( $\geq 18$  years) presented with a less severe phenotype compared with those younger, possibly indicating that individuals with more severe clinical symptoms are less likely to survive into adulthood or that paediatric care has improved. Individuals with a Late Truncating mutation had a less severe clinical presentation compared to those with an Early Truncating mutation. Mean severity scores for different precise mutations were not significantly different, but this could be due to the small number of cases with each mutation. Cases with R294X and R306C mutations tended to have lower severity scores. In contrast with other reports, the only case with R133C was associated with a severe clinical phenotype, generally reported to be a milder mutation. It is important to consider that these are only descriptive data and the small numbers of individual with each mutation prevent firm conclusions.

## CHAPTER 7

### CHARACTERISING THE BEHAVIOURAL PHENOTYPE OF RTT

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#### 7.1 Introduction

Previous studies have suggested that RTT is associated with a behavioural phenotype. Behavioural features reported most commonly include: hand stereotypies, breathing abnormalities, autistic features during regression and sleep disturbances. Some behaviours are reported to be specific to the syndrome such as hand stereotypies (hand clapping, wringing, washing, tapping, twisting etc). Breathing abnormalities (deep breathing, apnea, hyperventilation, valsava manoeuvre) and sleep disturbances (night wake, screaming/laughing during the night, day sleep) are also well documented in RTT. However, although a literature review indicated that these behaviours are frequently reported in RTT, studies did not have well matched control groups in order to establish whether these behaviours are specific features of the syndrome or more general problems due to severe ID. Other behaviours, such as self-injury, depression, repetitive behaviour and hyperactivity have received less research attention. Coleman et al. (1988) reported hyperactivity in a small percentage of a group of females with RTT while Mount et al. (2002a) reported a low level of hyperactivity in adults with RTT as measured by the Aberrant Behaviour Checklist. However, no other studies to my knowledge have yet reported similar data.

Impulsivity and overactivity are important to explore in those with severe/profound ID for their association with self-injury and aggression (Petty and Oliver 2005; Oliver et al. 2009). Luzzani et al. (2003) found a strong correlation between reflux and level of hyperactivity in a group of individuals with Cornelia De Lange syndrome, indicating

that hyperactivity could be an indicator of pain and discomfort. Depression in RTT has never been reported. Due to the severe/profound level of ID in this group, assessing depression is a challenge due to the fact that the person is not able to self-report feelings and emotions. The prevalence of mood disorder in individuals with severe/profound ID is thought to be between 1.3% and 3.7% (Deb et al. 2001), although it has been argued that these figures underestimate the true occurrence due to the fact that people with ID present with communication difficulties and may not be able to express their feelings. Depression in individuals with ID can present with typical and atypical symptoms including: screaming, aggression, self-injury, low mood and lack of interest (Marston et al. 1997; Meins 1995). Among the aims in the present research was to explore the concept of depression as conceptualized by Ross and Oliver (2002). Mood, interest and pleasure will be measured with the Mood Interest and Pleasure Questionnaire (MIPQ, Ross and Oliver 2003b).

The overall aim of this study was to characterize the RTT behavioural phenotype further in 91 females with a clinical diagnosis of RTT. The first part of the analysis provides a description of the adaptive and behavioural profile of the sample using the Vineland Adaptive Behavior Scale (VABS), Rett Syndrome Behavioural Questionnaire (RSBQ) and the Developmental Behavior Checklist (DBC). In addition, hyperactivity, depression, repetitive behaviour and self – injurious behaviours will be explored using The Activity Questionnaire (AQ), Mood, Interest and Pleasure Questionnaire – Short form (MIPQ – S), the Repetitive Behaviour Questionnaire (RBQ) and Challenging Behaviour Questionnaire (CBQ).

Due to the floor effect on the VABS, age equivalent scores will be reported and a qualitative description of the sample will be given. As the items in the motor skills domain assessed in the VABS are normally acquired by the age of six, the domain is not

normally administered to those age six and older unless a physical delay is suspected. However, if a motor skills deficit is suspected, as in the case of females with RTT, it is appropriate to administer the domain. However, the motor skills score for participants six years and older was not included when standard scores, age equivalents and adaptive levels were calculated. The motor skills domain was used to assess fine and gross motor skills in the sample.

Total and subscale scores for the RSBQ and DBC were analysed in relation to age group, age of regression, type of mutations, diagnostic categories, and severity of clinical phenotype. Scores of the DBC were analysed separately for the children and adults due to the fact that two different versions of the scale were used (DBC –P for children and DBC – A for adults). Identification of significant sub - groups with higher scores was carried out for the scales with the aim to identify characteristics of individuals with a severe behavioural profile.

For the AQ and RBQ, a total score excluding items that require verbal ability was employed for all participants (only 3 individuals were reported to speak or sign more than 30 words).

Where data were non-normally distributed, Kruskal-Wallis tests were carried out to explore differences between sub-groups. Post-hoc analyses (Mann-Whitney U tests) were carried out where significant differences emerged (correction of p value for post-hoc analysis depending on numbers of comparisons, i.e. for comparisons between age groups significance of p value would be 0.01).

## 7.2 Adaptive skills in RTT

Level of adaptive skills was measured with the VABS. The majority of the sample (84.5%; N = 71) scored <20 on the Adaptive Behaviour Composite, with only 15.5% (N = 13) scoring between 20 and 34 (group mean 24.92, SD 4.36). Descriptive analysis indicated that those with an Adaptive Behaviour Composite above 20 were children between the age of 4 -11 years old.

Analysis of the age equivalent scores revealed that the RTT sample had an equivalent age of below 12 months in the Adaptive Behaviour Composite, Communication, Socialisation and Motor skills domains. Only the Daily living skills domain was higher, although the age equivalent in this respect was just 12.7 months (see Table 7.1).

**Table 7.2 Adaptive skills in the RTT sample**

VABS Domains	Developmental Age equivalent (months)	
	Mean (SD)	Range
Adaptive Behavior Composite	10.52 (3.15)	4 – 23
Communication	9.90 (4.67)	1 – 34
Daily living skills	12.65 (3.91)	1 – 23
Socialization	8.96 (4.53)	1 – 23
Motor skills	5.52 (5.52)	1 – 23
Level of developmental delay	Profound 91.7% (77) Severe 8.3% (7)	

Data available for 84 participants and 80 for the motor skills domain

Correlation analysis showed significant positive associations between chronological age and daily living skills (age equivalent) and motor skills (age equivalent) (see Table 7.2). There were negative significant associations between the severity score and all VABS domains except for socialization skills. Older age of regression was associated with higher daily living and motor skills.

**Table 7.3 Correlation analysis of Age equivalent score in the VABS domains with chronological age, severity score and regression age**

VABS age equivalent	Chronological Age	Severity score	Age of regression (in months)
Adaptive behaviour composite	.122	-.326**	.095
Communication	-.032	-.321**	.077
Daily Living	.294**	-.554 <sup>#</sup>	.323***
Socialization	-.066	-.166	-.095
Motor	.235*	-.752 <sup>#</sup>	.333***

\*p < .05, \*\* p < .01, # p<.001, \*\*\*p< .005

In the communication domain most of the girls were reported to be able to indicate yes and no and a preference by eye pointing and/or gesture, listen to instruction, understand the meaning of yes/no and listen to a story or music. Few individuals were reported to be able to use symbols, understand people's names or associate a person with their photograph. Some could say a word if highly motivated (i.e. mamma, daddy, dinner, yes, no), though not consistently. Only one girl was able to speak in full sentences and ask questions. Two others were able to say three-four word phrases.

A profound level of deficit was consistently reported across all cases in the Daily Living skills domain. A small number were able to feed themselves using a spoon or/and a fork (16/84), drink from a cup with assistance (21/84) and suck from a straw (19/84). Toileting was done on a regular schedule and most wore nappies.

In the Socialization domain, parents reported basic interpersonal skills (showing affection to familiar people and laughing when praised) but very few had any play skills. None had the ability to play alone or with others.

Motor skills were very severely impaired in all participants. All participants performed worst in fine motor skills. Highest abilities in fine motor skills included the ability to pick up a small object with the hand. Almost none of the sample could use fingers to pick up a small object.

### 7.3 Rett Syndrome Behavioural Questionnaire (RSBQ)

The RSBQ was developed to assess RTT specific behavioural characteristics. Table 7.3 provides RSBQ total and subscale mean scores.

**Table 7.3 RSBQ total and subscales mean score**

RSBQ	Mean (SD)	Range
Total	42.31 (14.85)	12-78
General mood	6.48 (3.98)	0-16
Breathing problems	5.05 (3.06)	0-10
Hand behaviours	8.44 (2.36)	1-12
Repetitive face movements	2.91 (1.94)	0-8
Body rocking and expressionless face	5.41 (2.23)	1-12
Night time behaviours	1.74 (1.59)	0-6
Fear/anxiety	4.40 (2.24)	0-8
Walking/standing	1.31 (1.46)	0-4

Kruskal – Wallis analysis of variance revealed few significant differences in RSBQ scores across age categories, diagnostic categories, types of mutation or severity scores. Significant differences in the walking/standing domain were found by age of regression ( $\chi^2_{(3)} = 11.06, p > .01$ ) and severity score ( $U=319.50, z = - 5.676, p > .001$ ). Those with a less severe/mild phenotype (with a severity score  $\leq 9$ ) and those who had a regression between 19 and 36 months ( $U = 40.00, z = - 3.429, p < .001$ ) were more likely to score higher on items such as “walks with stiff legs” and “leans on objects and people”.

Exploration of the distribution of RSBQ<sup>7</sup> scores among the 8 most common single mutations (for distribution of the mutations across the sample see Chapter 6) indicated that mean scores varied between mutations. Cases with R255X and R106W were more likely to have more behavioural problems reported in nearly all domains. Cases with R294X and R306C had a higher score in the walking/standing domain and lower score

<sup>7</sup> A Kruskal – Wallis analysis of variance was performed excluding the two single mutations (R133C and R106W) with only 1 case each. Analysis did not reveal any significant differences across mutations.

in the breathing abnormalities domain. Cases with C-terminal and R294X mutation were more likely to have problems in General mood and with Fear/anxiety (Table 7.4).

**Table 7.4 Distribution of mean score among the 8 most common mutations**

Mutation (N=10)	RSB Q Total score	General mood	Breathing problem	Hand behaviours	Repetitive face movements	Body rocking and expressionless face	Night-time behaviour	Fear/anxiety	Walking/standing
T158M (4)	35.0	5.75	4.50	7.50	2.0	4.0	1.75	3.50	0.50
R168X (5)	43.2	6.60	4.80	9.60	3.60	5.40	2.0	3.60	1.0
R255X (5)	50.40	6.80	7.60	10.60	3.40	6.40	2.20	5.40	0.20
R360C (6)	36.0	5.50	4.16	8.0	1.50	4.66	1.50	3.16	2.16
R294X (5)	44.60	6.20	3.80	8.0	2.60	6.0	1.80	6.0	2.20
R270X (6)	37.66	4.50	5.16	8.33	3.66	4.66	1.0	3.33	1.66
R133C (1)	34.0	6.0	4.0	7.0	2.0	4.0	2.0	4.0	0.0
R106W (1)	58.0	7.0	9.0	11.0	6.0	7.0	2.0	4.0	0.0
C-terminal (13)	39.69	7.46	4.76	6.84	2.30	5.30	1.53	4.53	1.07
Other mutation (23)	39.80	5.72	4.92	8.52	2.60	4.76	1.32	4.36	1.24
No mutation (20)	49.05	7.89	5.36	9.0	3.78	6.68	2.52	4.84	1.63

#### 7.4 Behavioural and emotional problems in RTT

Data on behavioural and emotional problems were collected using the Developmental Behaviour Checklist (DBC). The DBC-Primary carer version was used for the children (< 18 years) and the Adult version for the adults ( $\geq$  18 years) within the sample. Hence, analysis will focus on describing behavioural and emotional problems associated with children and adults separately. Scores cannot be directly compared as assessments differ. The DBC – Adult version contains 12 extra items and changes were made to 7 items to reflect the adult population. Scores of 46+ for the child version and 51+ for the adult version are considered to be of clinical importance, thus indicating the

presence of behavioural/emotional disturbances. Mean Total Behaviour Problem Score (TBPS) and subscale scores were calculated and association with RTT characteristics explored (clinical severity of the phenotype, age of regression, mobility skills). Autistic symptoms were calculated using DBC-ASA only for the children. Table 7.5 shows total and subscale scores for the child and adult groups.

**Table 7.5 DBC scores in the children and adults**

	Children (n=41)		Adults (n=47)	
	Mean (SD)	Range	Mean (SD)	Range
DBC Total	26.8 (15.8)	5 - 64	26.4 (15.9)	4 - 75
Disruptive	3.7 (4.5)	0 - 17	3.7 (3.5)	0 - 13
Self-Absorbed	13.9 (7.4)	3 - 30	8.4 (3.8)	2 - 17
Communication disturbances	1.3 (1.6)	0 - 7	1.4 (2.1)	0 - 12
Anxiety	2.8 (2.8)	0 - 14	0.6 (0.9)	0 - 4
Social Relating	4.3 (2.6)	0 - 10	1.4 (1.5)	0 - 6
Depressive	-	-	4.1 (3.3)	0 - 12
ASA	11.3 (6.7)	0 - 26		

The children were divided into two age groups (participants below 12 years and participants between 12 and 17 years). Five (12.2%) children had a score of clinical significance on the TBPS of the DBC (mean 57.8, SD 6.57, range 47 – 64). Three were children below the age of 12 years. Four had a diagnosis of Classic RTT.

DBC total and subscales scores of the adults were also analysed. Three of the 48 participants in the adults group had a score of 51+, indicating the presence of behavioural and emotional problems of clinical importance. All three were between 18 and 25 years.

Correlation analysis between DBC (TBPS and subscales) and clinical severity of the phenotype revealed significant associations (see Tables 7.6a and 7.6b for correlation coefficients for children and adults). A higher number of significant associations were found among the children (in relation to the DBC total and the Disruptive, Self-

absorbed, Communication and Autism subscales). Among adults, the only significant association was with the Communication subscale.

**Table 7.6a Correlation coefficients between DBC total and subscales and severity score for the children (<18 years)**

	<b>DBC total</b>	<b>Disruptive</b>	<b>Self-Absorbed</b>	<b>Communication</b>	<b>Anxiety</b>	<b>Social</b>	<b>DBC - ASA</b>
Total severity Score	-.521*	-.550*	-.496**	-.538*	-.258	-.136	-.464**

\* p< .001; p< .005

**Table 7.6b Correlation coefficients between DBC total and subscales and severity score for the adults (>=18 years)**

	<b>DBC Total</b>	<b>Disruptive</b>	<b>Self-Absorbed</b>	<b>Communication</b>	<b>Anxiety</b>	<b>Social</b>	<b>Depressive</b>
Total severity score	-.132	-.122	-.106	-.399*	-.282	.013	.040

\* p< .01

Both children and adults were commonly rated at the highest level on items such as grinding teeth, laughing and giggling, facial twitches, mood changes, slow movement and repetitive hand movements, in line with behaviour expected to be found in those with RTT.

#### *7.4.1 Autistic symptoms in the Rett population*

The DBC-ASA was adopted in this study with the aim to (1) investigate the presence of autistic symptom in the sample, (2) explore differences/similarities (if any) between types of mutations and severity categories and (3) explore individual characteristics of those who display autistic behaviour compared to those who do not.

Further analysis aimed to explore whether Rett syndrome behavioural features, activity level, stereotyped behaviour and self-injury were associated with autistic features in the Rett sample. Analysis only included children. Although the 29 items forming the DBC-ASA are also present in the adult version, the validity of the autism algorithm in the adult version of the DBC has not yet been established. Brereton et al. (2002) found that the scale provides a good measure to discriminate between cases with and without autism among children with a sensitivity of 0.86 (95% CI 0.80-0.91) and specificity of 0.69 (95% CI 0.62-0.76).

The total score of the DBC-ASA for the 41 children ranged from 0 to 26 (mean 11.53, SD 6.53), with 12 participants (29.3%) scoring  $\geq 17$  (mean 20.00, SD 2.73).

Mann-Whitney analyses comparing the autistic (score  $\geq 17$ ) and non-autistic (score  $< 17$ ) groups indicated that children with ASD scored higher on the DBC total score and all subscales scores (see Table 7.7).

**Table 7.7 DBC total and subscale scores (Mean, SD, range) and Mann-Whitney test analyses between the autistic and non autistic groups**

	ASD (N = 12)	No ASD (N=29)	Mann Whitney U test		
			U	z	p
DBC TBPS	46.41 (12.47) 20 – 64	18.72 (7.87) 5 – 35	10.000	- 4.704	.000
Disruptive subscale	9.08 (4.39) 1 – 17	1.55 (2.02) 0 – 8	20.500	- 4.467	.000
Self-Absorbed subscale	23.00 (5.39) 13 – 30	10.10 (4.08) 3 – 19	15.000	- 4.565	.000
Communication disturbances subscale	2.16 (1.94) 1 – 7	0.89 (1.39) 0 – 4	79.000	- 2.878	.004
Anxiety subscale	4.91 (3.87) 0 – 14	1.93 (1.66) 0 – 6	85.000	- 2.595	.010
Social subscale	6.41 (1.62) 4 – 10	3.41 (2.38) 0 – 9	54.500	- 3.457	.000

Correlation analyses revealed negative significant associations between DBC – ASA scores and total severity scores ( $r = -.464$ ,  $p < .005$ ) and severity score walking domain scores ( $r = -.368$ ,  $p < .05$ ) and positive significant associations between DBC – ASA scores and occurrence of self-injury ( $r = .493$ ,  $p < .01$ ) and RSBQ total scores ( $r = .416$ ,  $p < .01$ ).

Although analyses of DBC-ASA scores between types of mutation and between single mutation groups did not reveal any significant associations, individuals with C-Terminal and Late Truncating mutation tended to have higher mean DBC-ASA scores (see Table 7.8 for mean DBC – ASA scores across types of mutation).

**Table 7.8 Mean, SD and range of DBC-ASA across types of mutations**

	Large Deletion (n=2)	C – Terminal (n=5)	Early truncating (n=18)	Missense (n=11)	Late Truncating (n=3)
DBC - ASA	6.50 (3.53) 4 – 9	13.20 (6.14) 7 – 21	9.33 (5.98) 0 – 23	11.27 (7.77) 1 – 26	20.00 (2.64) 17 – 22

### 7.5 Hyperactivity, depression and repetitive behaviour in RTT

Total scores for the AQ, MIPQ and RBQ varied across participants with RTT. Due to the small number of individuals with preserved speech, analysis of sub-scales that require the person to be verbal (i.e. Impulsive speech of the AQ, Restricted preferences and Repetitive speech of the RBQ) were not included in the analysis. Verbal and non-verbal individuals were included in the same analysis. Analysis focused on looking at differences between age groups and severity of the phenotype (mild  $\leq 9$ , severe  $>9$ ). Additionally, percentages of participants with low or high Mood and Interest and Pleasure were analysed to explore associations with autistic features and occurrence of self-injurious behaviours. The model in Oliver et al. (2001) was used in this study. For

the Mood subscale, scores of 15 (children  $\leq 18$  years) and 13 (Adults  $> 18$  years) are defined as low mood and scores of 24 (for both children and adults) are defined as abnormally high mood. For the Interest & Pleasure subscale, scores of 6 (for both children and adults) are defined as low interest & pleasure and scores of 23 (Children  $\leq 18$  years) and 21 (Adults  $> 18$  years) are defined as abnormally high.

Table 7.9 summarizes the means, standard deviations and ranges of total and subscale scores across age groups in the RTT sample.

**Table 7.9 Mean scores (SD) and score ranges on the AQ, MIPQ-S and RBQ across age groups with the results of Kruskal Wallis analyses of variance**

	<12 yrs (n=20)	12-17 yrs (n=23)	18-25 yrs (n=21)	>26 yrs (n=27)	Kruskal-Wallis		
	AQ				$\chi^2$	df	p value
Total (ALL participants)	22.5 (13.7) 3 - 52	10.86 (10.71) 0 - 43	12.26 (11.97) 0 - 44	13.9 (10.0) 0 - 42	11.458	3	.009
Overactivity sub-scale	12.85 (6.96) 3 - 31	7.39 (6.39) 0 - 23	6.50 (5.52) 0 - 22	8.29 (5.46) 0 - 22	12.480	3	.006
Impulsivity (mobile)	16.42 (3.59) 11 - 21	7.10 (6.52) 0 - 20	7.71 (7.15) 0 - 22	7.11 (6.09) 0 - 22	9.555	3	.023
Impulsivity (immobile)	6.11 (9.31) 0 - 24	0.69 (2.490) 0 - 9	1.07 (2.83) 0 - 7.5	2.50 (3.35) 0 - 9	5.064	3	.167
Impulsivity sub-scale (ALL participants)	9.72 (9.18) 0 - 24	3.47 (5.59) 0 - 20	5.50 (6.77) 0 - 22	5.57 (5.71) 0 - 22	6.049	3	.109
MIPQ-S							
MIPQ Total	36.80 (5.52) 23 - 45	31.39 (5.73) 22 - 44	33.09 (5.76) 19 - 40	34.07 (4.85) 24 - 44	10.620	3	.014
Mood sub-scale	20.55 (2.54) 13 - 24	18.08 (2.93) 12 - 23	18.71 (2.74) 11 - 22	18.46 (2.26) 14 - 22	12.367	3	.006
Interest & Pleasure	16.20 (3.76) 10 - 23	13.30 (3.64) 8 - 21	14.52 (3.89) 8 - 21	15.61 (3.02) 10 - 22	8.473	3	.037
RBQ							
RBQ total score (all sample)	8.35 (4.29) 4 - 18	6.65 (3.48) 0 - 12	8.31 (8.54) 0 - 41	6.48 (4.94) 0 - 24	2.739	3	.435
Stereotypies	6.65 (2.90) 4 - 12	5.78 (2.98) 0 - 12	5.54 (2.85) 0 - 12	4.59 (2.85) 0 - 12	5.049	3	.168
Compulsive	0	0	0.77 (3.62) 0 - 17	0.11 (0.57) 0 - 3	1.884	3	.597
Insistence on Sameness	1.20 (1.88) 0 - 4	0.34 (1.15) 0 - 15	0.77 (1.87) 0 - 8	0.81 (2.09) 0 - 8	3.458	3	.326

Mood and activity levels differed across age groups. *Post-hoc* analysis revealed that children aged under 12 years were more likely to have higher AQ total ( $U= 113.0$   $z= -2.852$ ,  $p< .005$ ) and overactivity subscale ( $U= 113.0$   $z= -2.806$ ,  $p< .01$ ) scores compared

to the adolescent group (12 – 17 years old). Moreover, significant differences were found between children aged under 12 years and those aged 18 – 25 years in relation to the AQ total score ( $U= 103.0, z= - 2.632, p< .01$ ) and overactivity subscale ( $U= 93.5 z= -3.047, p< .005$ ). Statistical analysis of the impulsivity subscale score (mobile) just failed to approach significance for the 18 – 25 years old group ( $U= 16.0, z= -2.344, p .019$ ) but was significant for the 26 years and older group ( $U= 14.5, z= -2.867, p< .005$ ). Significant group differences were also found on the MIPQ - S Total score and Mood and Interest/Pleasure subscales scores. Children below the age of 12 had a higher score on the MIPQ – S total score ( $U = 103.0 z = -3.103, p< .005$ ) and on the Mood ( $U = 109.0 z = -2.972, p< .005$ ) and Interest/Pleasure ( $U = 122.5 z = -2.628, p< .01$ ) subscales scores compared to the adolescent group (12 – 17 years old). Moreover, children (< 12 years) scored higher on the Mood subscale than older adults (26 years and older;  $U = 123.5 z = -3.054, p< .005$ ).

The relationship between severity of clinical symptoms (as measured by the Severity Score) and presentation of behavioural features was also explored. Mann Whitney tests revealed significant differences in the AQ total score ( $U= 409.0, z= - 4.663, p< .001$ ), overactivity subscale score ( $U = 608.5, z= - 3.204, p< .005$ ) and impulsivity subscale score (mobile,  $U=20.0, z= -2.562, p< .05$ ; all participants;  $U = 354.5, z = - 5.257, p< .001$ ), with those with a less severe/milder phenotype having higher scores. Those able to walk were more likely to have higher scores on the AQ Total ( $U= 505.0 z= -4.087, p< .001$ ) and overactivity scales scores ( $U= 759.0 z= -2.189, p< .05$ ). No significant differences were found across severity categories in the level of mood.

There were no significant differences in repetitive behaviour scores across age groups. However, correlation analysis indicated a negative significant association

between those with a less severe phenotype and total repetitive behaviour score ( $r = -.265, p < .05$ ).

Behaviours on the RBQ rated once a day and more than once a day are deemed to be of clinical importance (Moss et al. 2009). Table 7.10 shows percentages of RTT participants who were rated as showing behaviour rated at these frequencies. Inspection of the table indicates that level of hand stereotypy was 5 times higher than that of other stereotypies (objects and body stereotypies). This finding reflects the common understanding that hand stereotypies are characteristic features of the syndrome.

**Table 7.10 Percentage (n) of RTT girls scoring above the clinical cut-off in the stereotyped, compulsive behaviour and insistence on sameness subscales of the RBQ**

		Once a day	More than once a day
Stereotyped behaviour	Object stereotypy	5.5% (5)	14.3 (13)
	Body stereotypy	15.4 (14)	15.4 (14)
	Hand stereotypy	7.7 (7)	73.6 (67)
Compulsive behaviour	Cleaning	-	1.1 (1)
	Hoarding	-	-
	Organizing objects	-	-
	Rituals	1.1 (1)	1.1 (1)
	Lining up objects	-	-
	Completing behaviour	-	1.1 (1)
	Spotless behaviour	-	-
Insistence on sameness	Preference for routine	2.2 (2)	13.2 (12)
	Just right behaviour	- (0)	2.2 (2)

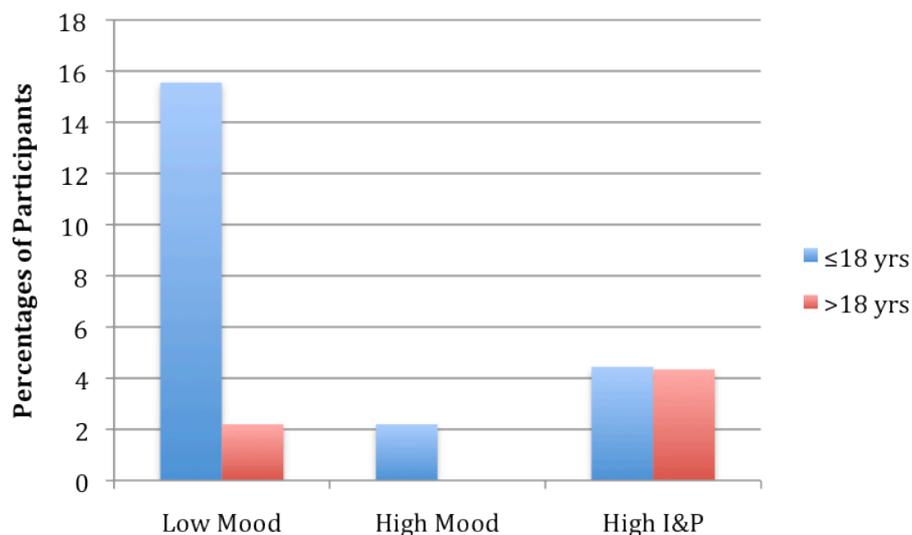
Correlation analyses between the RBQ and the autism subscales of the DBC amongst children were undertaken to assess whether those scoring higher on the RBQ overlapped with individuals in the ASD group. Significant positive associations were found for the Stereotyped behaviour ( $r = .425, p < .01$ ) and Insistence of sameness ( $r = .440, p < .005$ ) subscales. Moreover, correlation analyses at an items level revealed significant positive associations for object stereotypy ( $r = .355, p < .05$ ), body stereotypy

( $r = .338$ ,  $p < .05$ ) and preference for routine ( $r = .440$ ,  $p < .005$ ). Only 1 girl scored above the clinical cut off for items in the Compulsive Behaviour subscale: Cleaning, Rituals, Completing behaviours, and Spotless behaviour. This participant had a different profile from the other participants.

### 7.5.1 Abnormally low/high scores on the Mood, Interest and Pleasure questionnaire

The proportions of participants showing abnormally low/high scores on the Mood and Interests & Pleasure subscales are shown in Figure 7.1. There was no indication of low Interest & Pleasure in the sample, so the data are not displayed in the figure.

**Figure 7.1 Percentages of children ( $\leq 18$  years) and adults ( $> 18$  years) scoring abnormally high/low in the Mood and Interest & pleasure subscales of the MIPQ-S**



A greater number of children (15.6%,  $N=7$ ) aged 18 and younger showed low mood compared to adults (2.2%,  $N=1$ ). One participant in the children showed abnormally high mood. Similar proportions of abnormally high Interest and Pleasure were observed among children and adults.

Exploratory analysis did not show any association between low mood and presence of ASD features (measured with DBC-ASA). An equal proportion of participants in the

ASD and Non ASD group scored abnormally low on the mood subscale (ASD = 42.9, N=3; non ASD= 57.1%, N = 4;  $r = -.418$ ,  $p = .350$ ).

## 7.6 Occurrence and characteristics of self-injury and aggressive behaviours in RTT

Self-injurious behaviour was reported in 25 participants (27.5%). Twelve (48.0 %) of the 25 individuals reported to self - injure displayed one topography, 11 (44.0%) two topographies and the remaining two (8.0%) three topographies. Percentages of occurrence of different topographies of SIB are reported in Table 7.11. The most common ( $n=12$ , 48%) was rubbing or scratching self.

**Table 7.11 Topographies of Self-injury behaviour**

Rubs or scratches self	12 (48.0%)
Hits self with body part	8 (32.0%)
Bites self	8 (32.0%)
Hits self against surface	3 (12.0%)
Pulls hair or skin	5 (20.0%)
Inserts fingers or objects (i.e. eye poking)	1 (4.0%)
Other form	2 (8.0%)

The sample was divided into two groups: self-injury and non self-injury. Analysis was conducted to explore variation in age, severity of clinical phenotype, mobility, level of mood, overactivity and impulsivity between those with and without self-injury. Mann Whitney  $U$  tests revealed significant differences in total severity score ( $U = 540.50$ ,  $z = -2.541$ ,  $p < .01$ ), overactivity ( $U = 451.50$ ,  $z = -3.328$ ,  $p < .001$ ), impulsivity ( $U = 484.50$ ,  $z = -2.886$ ,  $p < .005$ ) and presence of RTT behavioural features as measured with the RSBQ ( $U = 565.00$ ,  $z = -2.231$ ,  $p < .05$ ), but not differences in age or level of mood. In relation to RSBQ domains, there were significant differences between the

groups with respect to RSBQ repetitive face movements ( $U = 547.00, z = - 2.421, p < .05$ ), RSBQ night-time behaviour ( $U = 521.50, z = - 2.690, p < .01$ ), RSBQ fear/anxiety ( $U = 547.00, z = -2.416, p < .05$ ) and RSBQ walking/standing ( $U = 591.000, z = - 2.128, p < .05$ ).

Aggression was reported in 8 (8.8%) of the sample. Differences between those reported to display aggression and those not displaying aggression were explored. Mann Whitney U tests revealed significant differences in total severity score ( $U = 108.50, z = - 3.126, p < .005$ ), ability to walk ( $U = 94.00, z = - 3.535, p < .001$ ), TAQ total score ( $U = 77.50, z = - 3.539, p < .001$ ), overactivity ( $U = 117.00, z = -2.999, p < .005$ ) and impulsivity ( $U = 94.50, z = - 3.381, p < .005$ ), indicating that those with a milder clinical phenotype and hyperactivity/impulsivity were more likely to display aggression.

## **7.7 Discussion**

Across the sample, a profound level of ID was consistently reported with all participants scoring  $<20$  on the adaptive behaviour composite of VABS. These results are consistent with other studies (Fontanesi and Haas 1988, Perry et al. 1991, Sandberg et al. 2000) indicating that individuals with RTT, in particular those with a more severe phenotype experience a profound level of impairment in adaptive skills.

Caution needs to be exercised when interpreting the VABS results. As most of the sample scored below 20, their scores suffer from a floor effect. Moreover, due to the developmental nature of the scale, raw scores near the floor can translate to somewhat higher summary scores. For example, a raw score of zero in some sub-domains could result in a non-zero age equivalent score (i.e. a raw score of 0 in the Domestic sub-domain of the Daily living skills results in an age equivalent score of 1 year and 6

months, as it is not expected that a child below that age would be able to perform such activities; Sparrow et al. 1984).

In the present sample, participants performed better in the daily living, with an age equivalent score of 12.7 months and had the greatest impairment in and motor skills domains. Other studies have suggested that age of onset and chronological age were associated with daily living skills (Perry et al. 1991) and that skills in general are retained at the developmental level of onset of the syndrome, which produces the association between later onset and better adaptive skills (Fontanesi and Haas 1988). This study also found that age equivalent scores in daily living and motor skills were correlated with age of regression. Correlation analysis also indicated that older individuals had better self-help and motor skills. However, this finding cannot be interpreted precisely. It could mean that individuals do make some progress over time and regain some of the skills lost after the regression stage. Alternatively, it could mean that individuals with a more severe phenotype do not survive into adulthood.

Analysis of the RSBQ found few significant differences between sub-groups based on age, type of mutation, diagnostic categories or age of regression. The exceptions were associations between the walking/standing domain score and the severity score and age of regression. Those girls with a milder phenotype and with a regression age between 19 and 36 months had higher walking/standing domain scores. Mount et al., (2002b) validated the RSBQ using a sample that only comprised children (< 19 years of age) and reported a mean total score of 45.2. Other studies (Robertson et al. 2006; Kaufmann et al. 2011) using the RSBQ to assess children with RTT have reported similar mean scores. For example, Kaufmann et al. (2011) investigated RTT-related behavioural problems in a sample of 80 children aged 1 – 14 years and found that RSBQ scores did not vary with age. This study extends this earlier literature by having a

mixed child and adult sample. It found a mean RSBQ total score similar to the child-only studies. It also failed to find a significant association with age.

Autistic behaviours were measured only among the children in the sample with the DBC-ASA. Albeit that Wulffaert et al. (2009) found that autistic behaviours were more frequent among the children (< 10 years) within their sample than among the adults, findings from this study agree with Kaufmann et al. (2011) that autistic behaviours among children do not vary with age. They were more frequently reported in those with a less severe phenotype. The ASD group had higher RSBQ scores, were more likely to self-injure and had a less severe phenotype. Moreover, children in the ASD group, as indicated by DBC-ASA, overlapped with those who showed preference for routine and object and body stereotypies as measured by the RBQ. Unlike other studies (see Kaufmann et al. 2011; Robertson et al. 2006), genotype-phenotype analysis did not reveal any association between specific mutations and behavioural problems as measured by the RSBQ and DBC. This may be due to the fact that the sample here had relatively few cases of each mutation. Thus, the following merely descriptive results need to be interpreted with great caution. Cases with C-Terminal, R255X and R294X mutations were more likely to walk and to have greater scores on the autistic subscale of the DBC, greater mood difficulties, and fewer stereotypic hand behaviours. Cases with R255X and R106W mutations were more likely to have problems related to the hands, face movements and breathing and night-time problems. Cases with R294X and R106W mutations were more likely to have problems related to mood and walking. Cases with R168X mutation were more likely to exhibit behaviours related to mood difficulties, hand stereotypies, face movements, body rocking and night-time problems.

One of the core diagnostic criteria for depression identified in the DSM-IV is low mood and lack of interest and pleasure. As highlighted by Ross and Oliver (2003), there

are several methodological problems in assessing mood disorders in individuals with severe and profound ID due to lack of specific validation of instruments for this client group, poorly defined items and to the reliance on self-report in traditional assessments (which is problematic in those unable to speak). The MIPQ is an informant based questionnaire with clearly defined behavioural items to assess affect and interest in individuals with severe and profound ID based on the core symptoms of depression as outlined in DSM-IV, low mood and low interest and pleasure. Results revealed significant differences in mood and interest/pleasure between age groups. Children consistently performed better than the adolescent and adult groups in relation to mood and interest/pleasure. There was no association with self-injury or clinical severity of the phenotype. Depression has never been studied in RTT and the results of this study are indicative that mood and interest/pleasure decline with age. However caution must be taken when interpreting these findings as these results are only preliminary and change over time cannot be reliably inferred from a cross-sectional study. Moreover, further studies should take into consideration other variables such as health problems or medication at the time of the investigation.

A standardized instrument was used to assess SIB and a quarter of the sample was found to self-injure. The most common categories of self-injury reported included scratching/rubbing, hitting with body parts and biting self. None of the participants hit themselves with objects probably due to the lack of hand skills. Presence of self-injurious behaviour was more likely among those with a severe clinical and behavioural presentation (as measured with the RSBQ). Moreover, self-injury was more frequent in those individuals rated as autistic according to the DBC-ASA. Two earlier studies (Coleman et al. 1988; Samson et al. 1993) reported higher occurrence of self-injurious behaviour in RTT samples than found here: among about 49% compared to 28%.

However it is difficult to ascertain from these studies whether the self-injury assessed was primarily self-harm or secondary to continuous hand movements.

One of the main purposes of the analyses conducted here was to gain an indication of whether the behavioural presentation of a group of females with RTT possibly changes over time. A cross-sectional study such as this cannot be definitive as a longitudinal element is required to be able to separate age from cohort effects. However, while there was no significant variation across age groups in behaviour problems, there was some indication of ageing affecting daily living and motor skills, mood and activity levels.

The next part of the analysis described in the following chapter will focus on differences/similarities between the RTT sample and a well-matched control group using measures of overactivity, impulsivity, mood, interest and pleasure, challenging and repetitive behaviour (i.e., the AQ, MIPQ, CBQ, RBQ - see chapter 5 - Methodology for a description of the groups). Following that, family characteristics are described and the association between measures of family experience and participant clinical severity explored.

## CHAPTER 8

# A COMPARATIVE STUDY OF IMPULSIVITY, OVERACTIVITY, DEPRESSION, CHALLENGING BEHAVIOUR AND REPETITIVE BEHAVIOUR IN A GROUP OF FEMALES WITH RETT SYNDROME AND OTHER GENETIC SYNDROMES

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### 8.1 Introduction

One of the aims of behavioural phenotypic research is to establish systematic behavioural variation between groups with different genetic syndromes (for a discussion of the concept of behavioural phenotype see Chapter 2). For example, a study by Oliver et al. (2011) has shown that individuals with Fragile X and Cornelia de Lange syndromes show high levels of ASD symptomatology, while excessive impulsivity and overactivity have been identified in individuals with Cri du Chat, Angelman, Fragile X and Smith-Magenis syndromes. Excessive positive affect has been found to be more likely in individuals with Angelman and Cri du Chat syndromes and excessive interest and pleasure more likely in individuals with Lowe syndrome. Negative affect was more likely in individuals with Cornelia de Lange syndrome. Other studies of behavioural phenotypes have identified specific behavioural and cognitive pathways in genetic syndromes. An association between repetitive behaviours and self-injury, self-restraint and hyperactivity have been identified in Cornelia de Lange syndrome (Hyman et al. 2002). Repetitive behaviour, such as preferences for routine and repetitive questions, was found to be more frequent in individuals with Fragile X and Prader-Willi syndromes (Moss et al. 2009). There also appear to be associations between specific phenotypes and health problems. Data from this study indicated that proportions of

individuals reported to have gastrointestinal, bowel, epilepsy and dental problems were high in RTT.

Hall et al. (2008) reported that individuals with Cornelia de Lange syndrome experienced significantly more eye, gastrointestinal and hernia problems during their lives compared to a group of individuals with ID of mixed etiology. Seizures/epilepsy, gastrointestinal and bowel problems are significant medical problems often reported in individuals affected by RTT syndrome and other syndromes associated with ID. For example, previous studies have reported occurrences of epilepsy between 60% and 82% of individuals with RTT (Jian et al. 2007; Glaze et al. 2010). Moreover, seizures are a common problem in those with Angelman syndrome with about 80% affected (Clayton-Smith and Laan 2003). Gastrointestinal problems are also common in RTT with some studies reporting gastro-oesophageal reflux (Kerr and Witt Engestrom 2001). Moreover gastro-intestinal problems are often reported in Cornelia de Lange syndrome, with an occurrence of 65% (Luzzani et al. 2003).

The importance of these comparative studies is to understand the bio-psychosocial pathways underlying behaviour and the potential for syndrome specific intervention.

The literature review (see Chapter 4) highlighted a general lack of studies exploring behavioural presentation in the RTT population compared to a well-matched control group. Most of the studies included healthy participants (for breathing abnormalities and sleep disturbances) or individuals with disabilities, but did not control for level of ID. This part of the study aims to explore behavioural phenotypic differences between the RTT sample and a group of females diagnosed with other rare genetic syndromes. It has a matched group design, controlling for general characteristics (chronological age, gender) and disability specific characteristics (e.g., level of adaptive behaviour in terms

of feeding, dressing and washing skills and language ability) (see chapter 5 for a description of the recruitment process and selection of the control group).

In addition to exploring variation between the RTT and the control group as a whole, a secondary analysis compared the behavioural features of the RTT sample and members of the control group with Angelman syndrome. The clinical phenotype of individuals with RTT and Angelman syndrome in the early years overlap. Both conditions present with developmental delay, severe communication impairments, seizures, microcephaly and gait and/or truncal ataxia. Watson et al. (2001) reported a mutation in the *MECP2* gene in 5 of a group of 47 patients with suspected Angelman syndrome.

The aim here is to position the RTT group in relation to other groups on behavioural characteristics relating to overactivity and impulsivity, mood and interest/pleasure, repetitive behavior and self-injurious behaviour.

## 8.2 Comparison of behavioural features between RTT and a control group

### 8.2.1 Participants

Table 8.1 summarizes demographic information on the RTT and control group.

**Table 8.1 RTT and control group descriptive data**

Characteristics	RTT (n=88)	Control (n=66)
Gender	100% F	100% F
Mean chronological age in years (SD, range)	20.3 (10.20, 4-47)	15.0 (10.02, 4-45)
Mobile	44 (50%)	35 (53%)
Feeding self not at all	55 (62.5%)	21 (31.8%)
Feeding self with help	33 (37.5%)	45 (68.2%)
Dressing self not at all	88 (100%)	66 (100%)
Washing self not at all	88 (100%)	66 (100%)
Verbal ability	0 (0%)	0 (0%)

A total of 154 participants were included in this study: 88 in the RTT group and 66 in the control group, all of whom were diagnosed with a genetic syndrome associated with a behavioural phenotype (see Chapter 5 for a list the genetic syndromes). All were females. None of the participants in the study had dressing or washing skills or verbal ability. Fifty percent of the RTT group and 53.0% of the control group were mobile. Although an attempt was made to match the two groups closely also for age and feeding skills, Mann Whitney *U* tests revealed significant differences between the two groups (age:  $U = 1911.50$ ,  $z = -3.626$ ,  $p < .001$  and feeding abilities:  $U = 2013.00$ ,  $z = -3.757$ ,  $p < .001$ ). Participants in the control group were more able to feed themselves with help and were slightly younger.

### *8.2.2 Hyperactivity, depression, level of mood and interest/pleasure and repetitive behaviours*

Table 8.2 summarises the results of the analyses.

**Table 8.2 Means (SDs) and ranges for the AQ, MIPQ and RBQ total and subscale scores**

	RTT (N=88)	Control (N=66)	Mann Whitney		
	AQ		U	z	p value
Total score	14.44 (11.94) 0 – 52	33.1 (14.92) 0 – 60	910.00	- 7.143	.000
Overactivity	8.57 (6.30) 0 – 31	18.7 (8.92) 0 – 37	1009.50	- 6.837	.000
Impulsivity	5.8 (7.03) 0 – 24	14.4 (7.91) 0 – 24	1193.00	- 6.143	.000
Impulsivity (immobile)	2.82 (6.0) 0 – 24	9.8 (7.67) 0 – 24	262.50	- 4.624	.000
Impulsivity (mobile)	8.62 (6.81) 0 – 22	18.6 (5.48) 6 – 24	207.00	- 5.534	.000
MIPQ					
MIPQ – S Total score	33.90 (5.76) 19 – 45	33.7 (7.79) 4.36 – 47	2813.00	- .052	.958
Mood	19.68 (2.50) 11 – 24	19.1 (4.19) 0 – 24	2753.00	- .279	.780
Interest and Pleasure	14.21 (4.09) 7 – 24	14.6 (4.57) 4 – 23	2676.50	- .564	.573
RBQ					
RBQ Total score	6.94 (4.31) 0 – 24	13.9 (7.67) 3 – 36	1134.00	- 6.011	.000
Stereotyped behaviour	5.53 (2.90) 0 – 12	8.8 (3.22) 0 – 12	1276.50	- 5.814	.000
Compulsive behaviour	0.03 (0.31) 0 – 3	1.5 (2.60) 0 – 12	1876.00	- 5.627	.000
Insistence of sameness	0.69 (1.64) 0 – 8	1.2 (2.09) 0 – 8	2474.00	- 1.749	.080

Significant differences were found between the RTT and control group on the Impulsivity and Overactivity subscales of the AQ, as well as the total overall. The RTT group scored significantly lower. This was true even for the Impulsivity subscale analysed separately for immobile and mobile participants. There were no significant differences between the RTT and control group on the MIPQ - S in total or on its Mood and Interest/Pleasure subscales. Analysis of the RBQ revealed significant differences between the two groups in all but the Insistence on Sameness subscale. The control group had higher scores on the Stereotyped and Compulsive behaviour subscales and the RBQ in total.

Table 8.3 reports numbers of individuals in the RTT and control group who scored above the clinical cut off on the RBQ (i.e., frequencies of once a day and more than once a day). Items analysis indicated significant differences in relation to Object stereotypies (U = 970.00 z= -7.392, p< .001), Body stereotypies (U =1447.00 z= -5.361, p< .001), Hand stereotypies (U =2380.50 z= -2.128, p< .05), Tidying up (U = 2728.00 z= -2.029, p< .05), Hoarding (U =2596.00 z= -2.898, p< .005), Attachment to objects (U= 1964.50 z= -3.904, p< .001), Repetitive phrases (U =229.50 z= -3.331, p< .005), Rituals (U= 2540.00 z= -2.892, p< .005), Completing behaviour (U= 2684.00 z= -2.350, p< .05) and Spotless behaviour (U= 2420.00 z= -3.791, p< .001). The control group scored higher on all items except for hand stereotypies.

**Table 8.3 Number (%) of RTT and control scoring Once a day and More than once a day on the RBQ items**

Items		RTT	Control
Object stereotypies	Once a day	5 (5.7%)	7 (10.6%)
	More than once a day	12 (13.6%)	42 (63.6%)
Body stereotypies	Once a day	14 (15.9%)	7 (10.6%)
	More than once a day	13 (14.8%)	34 (51.5%)
Hand stereotypies	Once a day	5 (5.7%)	10 (15.2%)
	More than once a day	66 (75.0%)	37 (56.1%)
Cleaning	Once a day	/	/
	More than once a day	/	1 (1.5%)
Tidying up	Once a day	/	/
	More than once a day	/	/
Hoarding	Once a day	/	1 (1.5%)
	More than once a day	/	3 (4.5%)
Organising objects	Once a day	/	/
	More than once a day	/	/
Attachment to objects	Once a day	6 (6.8%)	4 (6.1%)
	More than once a day	5 (5.7%)	19 (28.8%)
Repetitive phrases	Once a day	1 (1.1%)	2 (3.0%)
	More than once a day	3 (3.4%)	11 (16.7%)
Rituals	Once a day	1 (1.1%)	4 (6.1%)
	More than once a day	0	2 (3.0%)
Preference for Routine	Once a day	2	7 (10.6%)
	More than once a day	11	8 (12.1%)
Lining up objects	Once a day	/	1 (1.5%)
	More than once a day	/	/
Just right behaviour	Once a day	2 (2.3%)	2 (3.0%)
	More than once a day	1 (1.1%)	2 (3.0%)
Completing behaviour	Once a day	/	3 (4.5%)
	More than once a day	/	1 (1.5%)
Spotless behaviour	Once a day	/	1 (1.5%)
	More than once a day	/	4 (6.1%)

Percentages vary due to missing data

### 8.2.3 Occurrences of Self-Injurious behaviour

Self-injurious behaviours were reported in 24 (27.3%) of the RTT group and 18 (45.0%)<sup>8</sup> of the control group, a difference which was significant (Mann Whitney U = 1448.00,  $z = -1.972$ ,  $p < .05$ ). When topographies of SIB were analysed separately, the greater occurrence of SIB among the control group was clear (see Table 8.4). All topographies, except for rub/scratches, were more common in the control group.

<sup>8</sup> Data available on 85 individuals of RTT and 40 individuals of the control group

**Table 8.4 SIB topographies in the RTT and control group with statistical test results**

	RTT (n=24)	Control (n=18)	Mann Whitney U test		
			U test	z score	p value
Hit self with body part	8 (33.3%)	14 (55.6%)	1278.0	- 3.523	.000
Hit self against surface	3 (12.5%)	9 (38.9%)	1393.0	- 3.371	.000
Hit self with object	/	9 (50%)	903.0	- 6.906	.000
Bites self	8 (33.3%)	9 (50%)	1063.0	- 4.845	.000
Pull hair/skin	5 (20.8%)	15 (44.4%)	1175.0	- 4.513	.000
Rub/scratches	11 (45.8%)	12 (33.3%)	1444.0	- 2.127	.033
Insert objects	1 (4.1%)	4 (16.7%)	1568.0	- 2.356	.018

Percentages vary due to missing data

### 8.3 Comparison of behavioural features between RTT and Angelman syndrome

Comparison between the RTT and Angelman syndrome group on demographic variables revealed significant differences in age ( $U = 719.50$   $z = -2.634$ ,  $p < .01$ ) and feeding ( $U = 632.50$   $z = -3.741$ ,  $p < .001$ ), indicating that individuals in the Angelman syndrome were younger and had better feeding abilities than the RTT group (Table 8.5).

**Table 8.5 Demographic characteristics of the RTT and Angelman syndrome sample**

Characteristics	RTT (n=88)	Angelman (n=25)
Gender	100% F	100% F
Mean chronological age in years (SD, range)	20.3 (10.20, 4-47)	14.8 (10.70, 4-45)
Mobile	44 (50%)	13 (52%)
Feeding self not at all	55 (62.5%)	5 (20.0%)
Feeding self with help	33 (37.5%)	20 (80.0%)
Dressing self not at all	88 (100%)	66 (100%)
Washing self not at all	88 (100%)	66 (100%)
Verbal ability	0 (0%)	0 (0%)

Comparison between the RTT (n= 88) and Angelman syndrome group (n= 25) indicated that the RTT group scored significantly lower than individuals with Angelman syndrome with respect to: AQ Total, Impulsivity (mobile and immobile), Overactivity, MIPQ – S total, Mood subscale and the RBQ Stereotyped and Compulsive behaviour subscales (see Table 8.6).

**Table 8.6 Means (SDs) and ranges for the TAQ, MIPQ and RBQ total and subscale scores**

	RTT (N=88)	Angelman (N=25)	Mann Whitney		
	AQ		U	z	p value
AQ Total	14.44 (11.94) 0 – 52	35.57 (14.49) 4 – 59	290.00	-5.576	.000
Overactivity	8.57 (6.30) 0 – 31	19.77 (8.54) 4 – 35	307.00	-5.494	.000
Impulsivity (All)	5.8 (7.03) 0 – 24	15.80 (7.87) 0 – 24	66.50	-4.221	.000
Impulsivity (immobile)	2.82 (6.0) 0 – 24	12.00 (8.86) 0 – 24	77.00	-4.094	.000
Impulsivity (mobile)	8.62 (6.81) 0 – 22	19.30 (4.93) 6 – 24	386.00	-4.977	.000
MIPQ					
MIPQ – S Total score	33.90 (5.76) 19 – 45	36.67 (7.66) 16 – 47	761.00	-2.286	.022
Mood	19.68 (2.50) 11 – 24	21.15 (3.50) 9 – 24	620.00	-3.295	.001
Interest and Pleasure	14.21 (4.09) 7 – 24	15.52 (5.05) 6 – 23	901.50	-1.303	.193
RBQ					
RBQ Total score	6.94 (4.31) 0 – 24	11.54 (5.16) 3 – 25	429.00	-3.979	.000
Stereotyped behaviour	5.53 (2.90) 0 – 12	9.17 (2.83) 3 – 12	388.50	-4.605	.000
Compulsive behaviour	0.03 (0.31) 0 – 3	0.83 (1.43) 0 – 4	760.00	-4.701	.000
Insistence of sameness	0.69 (1.64) 0 – 8	0.58 (1.21) 0 – 4	1039.00	-0.175	.861

Items analysis revealed significant differences in relation to Object stereotypies (U= 337.00, z= -5.419, p< .001), Body stereotypies (U= 554.50 z= -3.571, p< .001) and

Spotless behaviour ( $U= 880.00$   $z= -4.271$ ,  $p< .001$ ), with the Angelman syndrome group having higher scores than the RTT group.

**Table 8.7 Number (%) of RTT and Angelman syndrome scoring Once a day and More than once a day on the RBQ items**

Items		RTT	Angelman
Object stereotypies	Once a day	5 (5.7%)	4 (16.0%)
	More than once a day	12 (13.6%)	13 (52.0%)
Body stereotypies	Once a day	14 (15.9%)	3 (12.0%)
	More than once a day	13 (14.8%)	12 (48.0%)
Hand stereotypies	Once a day	5 (5.7%)	4 (16.0%)
	More than once a day	66 (75.0%)	16 (64.0%)
Cleaning	Once a day	0	0
	More than once a day	0	0
Tidying up	Once a day	0	0
	More than once a day	0	0
Hoarding	Once a day	0	0
	More than once a day	0	0
Organising objects	Once a day	0	0
	More than once a day	0	0
Attachment to objects	Once a day	6 (6.8%)	1 (4.0%)
	More than once a day	5 (5.7%)	4 (16.0%)
Repetitive phrases	Once a day	1 (1.1%)	1 (4%)
	More than once a day	3 (3.4%)	1 (4.0%)
Rituals	Once a day	1 (1.1%)	1 (4.0%)
	More than once a day	0	0
Preference for Routine	Once a day	2	2 (8.0%)
	More than once a day	11	1 (4.0%)
Lining up objects	Once a day	0	1 (4.0%)
	More than once a day	0	0
Just right behaviour	Once a day	2 (2.3%)	0
	More than once a day	1 (1.1%)	0
Completing behaviour	Once a day	0	0
	More than once a day	0	0
Spotless behaviour	Once a day	0	1 (4.0%)
	More than once a day	0	1 (4.0%)

### 8.3.1 Occurrences of Self-Injurious behaviours

Similar proportions of the RTT and Angelman groups had self-injurious behaviour, albeit that data were only available for 9 individuals in the latter group. Significant differences were found when topographies of self-injurious behaviours were analysed separately, in relation to: hits self with objects (Angelman syndrome: 16.0% RTT 0%;

$U = 215.00, z = - 6.283, p < .001$ ) and pulls hair/skin (Angelman syndrome: 12.0%, RTT: 5.7%;  $U = 280.50, z = - 2.814, p < .01$ ). No significant differences were found in other topographies.

#### **8.4 Discussion**

In this chapter, the differences between a group of females with RTT and females with a mixture of genetic syndromes were examined with the aim to identify phenotypic differences between groups on measures of impulsivity and overactivity, mood, repetitive behaviour and self-injurious behaviours. In addition, analysis including comparison to an Angelman syndrome group only.

Comparative analyses of their behavioural phenotypes revealed several important findings. Firstly, females with RTT were characterized by a low level of impulsivity and overactivity. These results are probably due to the severe physical disability of the RTT group. Second, females with RTT were characterized by a low level of mood compared to the Angelman syndrome group. Previous studies have indicated that individuals with Angelman syndrome are characterized by excessive positive affect and impulsivity and overactivity (Horsler and Oliver 2006; Oliver et al. 2011). Hence, mood may not be irregular in RTT and it was shown to be no different to that in the wider control group.

Repetitive behaviour was also low compared to the control and the Angelman syndrome groups. Analysis of subscales and at an items level indicated that the RTT group had a very low specific profile on the repetitive behaviour scale, including stereotyped behaviour other than hand stereotypies. One of the behavioural features of RTT is the presence of repetitive hand stereotypies. Hand stereotypies were found to be distinctive of RTT when compared to the control group of mixed genetic syndromes. However, they were not found to be distinctive of the RTT group when compared to the

Angelman syndrome group. Moss et al. (2009) reported a low level of hand stereotypies and low level of repetitive behaviour in the Angelman syndrome group. The data here relate to a subgroup with low adaptive behaviour consistent with the general ability of individuals with RTT. Hence, the relationship between the presence of hand stereotypies and adaptive behaviour within Angelman syndrome might be investigated further. Moreover, qualitative observation is required to explore possible differences in hand stereotypies between the two groups. Other studies (Percy et al. 1988; Goldman and Tremudo 2012) have compared the hand stereotypies of children with RTT and children with autism. It was clear that the stereotypies of RTT are different, monotonous and generally localized in the midline. Moreover, the stereotypies of children with autism are more complex and often involve objects. This was the first study to compare hand stereotypies among RTT and individuals with diagnoses other than autism.

Finally, occurrence of self-injurious behaviour among the RTT group was less than the control group but similar to the Angelman syndrome group. All topographies of self-injury, a part for rubbing and scratching were more common among the control group and two were more common among the Angelman syndrome group. Topographies of self-injury dependent on object manipulation would be unlikely to be seen in RTT due to the typical lack of hand skills.

This is the first large study to my knowledge that explores impulsivity, overactivity, mood, repetitive behaviour and self-injurious behaviours in RTT using a matched control group of individuals with mixed genetic syndromes. Moreover this is the first study that has explored behavioural phenotypic differences between RTT and Angelman syndromes. Further studies should explore mood and interest/pleasure in more detail and in particular examine how hand stereotypies differ across the

syndromes using more detailed behavioural observation methods and determine if and how these are influenced by the environment.

**CHAPTER 9**

**ANALYSIS OF THE PSYCHOLOGICAL WELL-BEING AND  
ADJUSTMENT OF FAMILIES WITH A DAUGHTER WITH RETT  
SYNDROME**

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**9.1 Introduction**

It is now well documented that parents of children with a lifelong disability experience greater stress, anxiety and depression than parents with normally developing children (Beckman 1991; Dumas et al. 1991; Dyson 1991; Emerson 2003; Friedrich and Friedrich 1981; Hastings and Beck 2004; Hastings 2005). Themes investigated include: level of stress, social isolation, anxiety and depression, relationship between family functioning and child behaviour (i.e. parent-child interaction, maternal expressed emotion), socio-cultural and economic environment and the impact that raising a child with ID has on different members of the family (i.e. fathers, siblings, grandparents and adoptive parents).

The family environment is important for child development. Research has highlighted that a positive, cohesive and supportive environment can lead to better outcomes for family adaptation and better development opportunities for the child with ID and siblings (Head and Abbeduto 2007). Children living in a family with greater cohesiveness and connectedness were found to have fewer behavioural problems over a five-year period (Warfield 1995) and more positive social emotional functioning (Mink et al. 1983). Moreover, interaction between child and mother has been found to be predictive of child cognitive and communicative skills (Barnard 1997). Hauser-Cram et al. (1999) investigated the relationship between

family environment and the development of adaptive skills in children with Down syndrome over 5 years. Results showed that children in positive family environments developed at faster rates than children in less positive environments.

The association between characteristics of the child with ID and family functioning has also been widely investigated. Although results are not entirely consistent, in general, research shows that the child's age, type of disability, and the behavioural and clinical severity of the condition have an impact on family adaptation and psychological well-being. Type of disability of the child has the potential to have a differential impact on family well-being. Parents of children diagnosed with an autistic spectrum disorder are reported to experience a high level of stress and depression, social isolation and pessimism about the future (Abbeduto et al. 2004; Head and Abbeduto 2007; Hastings et al. 2005; Schieve et al. 2007). Abbeduto et al. (2004) examined the psychological well-being of a group of mothers with a child diagnosed with Fragile X syndrome, Down syndrome or autism. The authors hypothesized that mothers with a son/daughter with Fragile X syndrome would experience similar psychological distress to mothers of individuals with autism, while mothers of offspring with Down syndrome would fare better. They found that mothers of individuals with Down syndrome were less pessimistic about the future and had a closer relationship with their child/adolescent compared to those with a son/daughter with autism or Fragile X syndrome. Mothers of individuals with autism reported more symptoms of depression compared to mothers with a child with Down syndrome, while mothers of individuals with Fragile X syndrome did not differ from the other two groups. Griffith et al. (2011) compared the psychological well-being of parents of children diagnosed with Angelman, Cri du Chat or Cornelia de Lange syndromes. Results showed that mothers of children with Angelman

syndrome were more likely to report a high level of anxiety compared to mothers of children with Cri du Chat and Cornelia de Lange syndromes. Similarly, fathers of children with Angelman syndrome were more likely to report a high level of anxiety compared to those with children with Cornelia de Lange syndrome. Both mothers and fathers of children with Angelman syndrome were more likely to report a high level of stress compared to parents of children with Cri du Chat and Cornelia de Lange syndromes.

Type and quality of support has been associated with family adaptation and well-being. Some parents cope better than others and experience lower levels of stress, depression and anxiety and are able to maintain a healthy psychological and physical well-being. There is much to understand concerning why some parents cope better than others. Variables such as gender (variability of stress in mothers and fathers), coping style and genetic structure have been found to influence why some parents cope better than others. In general, studies have demonstrated that mothers experience greater levels of stress and depression and increased caregiving responsibilities compared to fathers (Head and Abbeduto 2007). However, Hastings (2003) found little difference in the well-being of mothers and fathers of children with autism, albeit that mothers reported more symptoms of anxiety.

Coping style has also been linked to parental well-being. A problem-focused coping style involves the use of behavioural and cognitive strategies to address stressful situations, while an emotion-focused coping style involves the use of strategies to deal with negative emotions such as denial, avoidance and escape (Head and Abbeduto 2007; Kim et al. 2003). Cross-sectional and longitudinal studies have reported that parents who use an emotion-focused coping style experience poorer levels of well-being. The use of emotion-focused strategies is a

predictor of lowered well-being (Kim et al. 2003). Abbeduto et al. (2004) reported a higher level of pessimism in mothers who use an emotion-focused coping style than those who engaged in problem-focused coping. Mothers who used a problem-focused coping style reported greater closeness to the child with disability.

In addition, variation in the genotype may account for the poor level of well-being in some families. For example, mothers of children with Fragile X syndrome, who are themselves a carrier of a permutation or full mutation in the *FMR1* gene, may be at risk for depression, anxiety and social interaction difficulties (Head and Abbeduto 2007).

Different theoretical models have been put forward to explain parental stress and coping strategies. The Double ABCX model (McCubbin and Patterson 1984) conceptualized the family's stress, crisis and adaptation process as a dynamic and ongoing process, where A represents the stressor event, B the family's resources, C the interpretation of the crisis and X the crisis itself and adaptation process. The ability to cope with a stressor event interacts with other factors such as family support systems, resources, parental perception of the event, coping and adaptation strategies. The combination of elements will determine the level of adaptation, which is seen as a continuous process that can encompass positive and negative adaptation. Several studies have applied this model to explain stress and coping in families with a child with ID. Saloviita et al. (2003) investigated the effect of selected variables (family demands of having a child with ID, adaptive resources and definition of the situation) on the stress of mothers and fathers. Results indicated that the resources available and the meaning that the parents attributed to events had a larger effect on parental stress than child characteristics. Jones and Passey (2004) found that family coping strategies, social support and parental locus of control were

the variables most associated with parental stress, highlighting the importance of coping strategies and social support in mediating parental stress. Lack of understanding or knowledge about the disability and dealing with relatives and friends were both found to be extremely stressful by the majority of parents.

More recently, research has also focused on the positive experiences of families with a child with ID. Positive transformations (Scorgies and Sobsey 2000), increased happiness, family closeness and strength (Behr et al. 1998), stimulation of personal growth (Greer et al. 2006), pleasure and satisfaction in caring for the child and increased opportunity to learn and develop (Hastings and Taunt 2002) are some of the themes reported in the literature. Families with children with ID report both positive and negative experiences and there is evidence of an association between family variables (i.e. parent gender, age) and positive and negative perceptions. Moreover, studies comparing families with and without a child with ID have reported contrasting findings. It has been shown that families with a child with ID report more positive experiences (Hastings and Taunt 2002) and some other studies have suggested that positive perceptions of having a child with ID serve as a coping strategy. However, further studies are needed to test this proposition. Moreover, longitudinal studies to explore how parents' psychological well-being and positive perception changes and whether positive experience may be a moderator of stress are also needed.

## 9.2 Family studies on RTT

Despite a large body of research on the families of children with ID in general, studies exploring the health and mental health of families with children with RTT are rare. Only two such studies were found in a literature review, none of which included participants with RTT over the age of 19 years.

Perry et al. (1992) explored family stress, family functioning and adjustment in 29 families with a child with RTT. Results indicated that these families experienced a high level of stress, social isolation, health problems and stress in their relationships. These families also reported more cohesion, family organization and religious belief compared to a normative sample. The RTT child's age and the age of onset of RTT symptoms were related to family stress and functioning. Parents of older girls and those with a later onset experienced greater marital and family problems. Laurvick et al. (2005) explored family characteristics that are positively associated with good maternal physical and mental health. They found that factors such as feeding, sleep and behaviours such as repetitive face movements (i.e., mouth grimaces, repetitive tongue movements) were most likely to affect maternal mental and physical health. Level of functional independence was not associated with maternal physical or mental health (other studies with children with other conditions find similar results). Behavioural features, in particular face movements, were associated with poorer maternal mental health. The authors comment that this relationship could be linked to social convention; the behaviour is considered to be unacceptable and, therefore, the mother becomes stressed. However, such behaviours could also be a marker of the neurological severity of the phenotype overall. Consistent with this, maternal physical health was better if their child had not experienced breathing abnormalities or had a fracture in the last 2 years.

### **9.3 Aims of the study**

The aims of this study were to describe family stress, anxiety, depression and positive experiences (positive gains and feelings) amongst parents with a daughter with RTT and to relate these to child characteristics. Due to the small numbers of fathers participating in the study, analysis could not explore differences between mothers and fathers. Thus, the study focused on three aspects of the family experience:

1. The relationship between the characteristics of the child with RTT (age, severity of clinical and behavioural phenotype) and the family's positive and negative experiences.
2. The association between the family's positive and negative experiences.
3. The association between parental perception of progression/regression of behavioural and clinical symptoms and the family's positive and negative experiences.

Only families with a daughter with RTT living at home were included in the analysis. Measures employed are described in Chapter 5. They include the Questionnaire on Resources and Stress – short form (QRS - F), the Hospital Anxiety and Depression Scales (HADS), the Positive Gains Scale (PGS) and the Positive Affect Scale (PAS) as well as a novel questionnaire to explore parental perception of progression/ regression of behavioural and clinical symptoms.

### **9.4 Results**

A total of 80 families were included in this study. Seventy-four participants (92.5%) were mothers, 3 (3.8%) were fathers, 2 (2.5%) were foster mothers and 1 (1.2%) an adoptive mother. Parents' ages ranged between 30 and 71 years (mean

51.1, SD 9.33). Mean age of mothers was 49.8 years (SD 9.14, range 30 - 71) and mean age of fathers was 52.8 years (SD 10.08, range 30 - 78). 72.5% of parents were married and lived with their spouse, 10.1% lived with a partner and 17.5% were divorced/widowed/ separated/single and not living with a partner<sup>9</sup>.

Table 9.1 summarises the mean scores on the Questionnaire on Resource and Stress – short form (QRS - F), Hospital Anxiety and Depression Scales (HADS), Positive Gains Scale (PGS) and Positive Affect Scale (PAS), with SDs and ranges.

**Table 9.1 Mean (SD) and range of the family scales**

	<b>QRS – F Stress</b>	<b>HADS Anxiety</b>	<b>HADS Depression</b>	<b>PGS</b>	<b>PAS</b>
Mean	6.9 (3.27)	7.7	4.5	4.7	34.9
(SD)	0 – 13	(3.50)	(3.17)	(4.26)	(7.35)
Range		0 – 14	0 – 15	0 – 18	16 – 49

Mean scores on the Questionnaire on Resources and Stress (QRS – F) were 7.05 (SD 3.25, range 0 – 13) for the mothers and 4.0 (SD 3.0, 1 – 7) for the fathers. Mean scores on the HADS anxiety subscale were 7.7 (SD 3.48, range 0 - 14) for mothers and 6.0 (SD 4.35, range 3 - 11) for fathers. Eighteen out of the 77 mothers and 1 out of the 3 fathers had a score  $\geq 11$  on the HADS anxiety subscale (total n = 19, 20.9%). Mean scores on the HADS depression subscale were 4.6 (SD 3.18, range 0 – 15) for mothers and 3.3 (SD 2.88, range 0 – 5) for fathers. Four mothers and none of the fathers had a score  $\geq 11$  on the HADS depression scale (total n = 4, 4.9%). Mean scores on the Positive Gains Scale (PGS) and Positive Affect Scale (PAS) were 4.7 (SD 4.27, range 0 – 18) and 35.1 (SD 7.36, range 16 – 49) for mothers and 5.33 (SD 4.72, range 0 – 9) and 31.33 (SD 7.37, range 23 – 37) for fathers.

<sup>9</sup> For demographic information on all of the sample (n = 91) see chapter 6, Table 6.1

Correlation analysis indicated that parents' age was negatively correlated with level of parental stress as measured with the QRS-F ( $r = -.257, p < .05$ ), indicating that younger parents experienced a higher level of stress.

The first aim of the study was to analyse the relationship between the characteristics of the child/adult with RTT (age, behavioural presentation and severity of clinical phenotype) and family stress, anxiety and depression and positive gain and affect. Table 9.2 shows the distributions of the family scale scores across the four offspring age groups used previously. Scores on the QRS – F, HADS, PGS and PAS did not significantly differ according to the age group of the daughter with RTT and nor did the proportions of parents reporting high levels of stress, anxiety or depression.

**Table 9.2 Mean (SD) and range of family scale scores across the age groups of the RTT offspring**

	<12 yrs (N = 20)	12 – 17 yrs (N = 22)	18 – 25 yrs (N = 17)	26+ yrs (N = 21)
QRS – F	7.3 (2.95) 7 – 13	7.0 (3.51) 1 – 12	6.7 (3.45) 0 – 13	6.8 (3.37) 1 – 13
HADS Anxiety	8.3 (3.59) 2 – 14	8.5 (3.31) 3 – 14	7.9 (3.67) 1 – 13	6.1 (3.20) 0 – 13
HADS Depression	4.8 (3.01) 0 – 12	5.1 (3.32) 0 – 12	4.4 (3.01) 0 – 9	3.7 (3.30) 0 – 15
PGS	4.0 (3.58) 0 – 10	4.8 (3.81) 0 – 13	5.1 (4.85) 0 – 18	5.1 (4.95) 0 – 13
PAS	36.7 (6.67) 21 – 47	33.6 (6.71) 16 – 45	32.8 (7.28) 18 – 48	36.4 (8.43) 23 – 49

In general, family problems were found to be related to the behavioural presentation of the family member with RTT, as measured by the RSBQ. Stress (QRS – F scores) was related to the RSBQ Total ( $r = .266, p < .05$ ) and the General Mood ( $r = .354, p < .005$ ) and Fear /Anxiety ( $r = .246, p < .05$ ) subscales. HADS

Anxiety subscale scores were related to the RSBQ Total ( $r = .302, p < .01$ ) and the General Mood ( $r = .236, p < .05$ ), Repetitive Face Movements ( $r = .229, p < .05$ ) and Fear / Anxiety ( $r = .366, p < .005$ ) subscales. HADS Depression subscale scores were related to the RSBQ Total ( $r = .258, p < .05$ ) and the General Mood ( $r = .340, p < .005$ ) and Body Rocking and Expressionless Face ( $r = .231, p < .05$ ) subscales. However, there were no significant associations between severity of behavioural problems (i.e., RSBQ total and subscale scores) and positive gain and affect scores.

There were also no significant associations between any of the family scale scores and the clinical severity of the phenotype (as measured by the Severity score), except for an inverse association between the scoliosis subscale score and positive affect (PAS;  $r = -.236, p < .05$ ) (See *Appendix F – 1- F – 4: correlation coefficients for Family measures*).

#### *9.4.1 Association between level of stress, anxiety and depression and positive impact in family with a child/adult with RTT*

The second aim was to investigate the association between positive experience and negative impact. Correlation analyses revealed a significant negative association between PAS and QRS - F ( $r = -.342, p < .005$ ), HADS Anxiety ( $r = -.412, p < .001$ ) and HADS Depression ( $r = -.589, p < .001$ ) and a significant positive association between PGS and QRS – F ( $r = .290, p < .01$ ). These results indicate that parents experiencing high levels of stress, anxiety and depression were less likely to have positive feelings and parents experiencing a high level of stress were less likely to report a positive gain from having a daughter with RTT.

#### 9.4.2 Parents perception of regression/progression of skills

The third aim of the study was to investigate the relationship between both positive experience (as measured with the PGS and PAS) and negative impact (as measured with the QRS – F, HADS) and parental perception of regression and progression of behavioural and clinical presentation over time. Analysis of parental perception of progression and regression indicated that in all domains the greatest number of parents (48.4% or more) reported that behavioural and clinical presentation remained static. Moreover, apart from communication and body rocking, higher proportions of parents reported a worsening of behavioural and clinical presentation than reported improvement. Communication was reported as improving by 33% of parents and body rocking was reported as not a problem by 17.6% of parents (see Table 9.3).

**Table 9.3 Parents' perception of progression/regression of skills**

	<b>Getting worst</b>	<b>Staying the same</b>	<b>Getting better</b>	<b>Not a problem</b>
Breathing abnormalities	19 (20.1%)	61 (67.0%)	9 (9.9%)	1 (1.1%)
Physical robustness/fitness	34 (37.4%)	44 (48.4%)	13 (14.3%)	0
Mobility/walking	38 (41.8%)	44 (48.4%)	6 (6.6%)	3 (3.3%)
Communication	2 (2.2%)	59 (64.8%)	30 (33.0%)	0
Purposeful hand use	16 (17.6%)	69 (75.8%)	6 (6.6%)	0
Repetitive hands movements	12 (13.2%)	69 (75.8%)	10 (11.0%)	0
Body rocking	5 (5.5%)	59 (64.8%)	10 (11.0%)	16 (17.6%)
Mood changes	16 (17.6%)	57 (62.6%)	13 (14.3%)	3 (3.3%)
Problems with anxiety	14 (15.4%)	58 (63.7%)	11 (12.1)	6 (6.6%)
Night-time behaviours	13 (14.3%)	65 (71.4%)	10 (11.0%)	1 (1.1%)
Feeding problems	23 (25.3%)	55 (60.4%)	11 (12.1%)	2 (2.2%)

Scoring deterioration as -1, no change as 0, improvement as 1 and not a problem as 2, the total scores across all domains for parental perception overall ranged from -9 to +11 (mean -0.17, SD 3.93), reinforcing the general impression of no change across the sample.

Correlation analyses revealed significant negative associations between the overall parental perception score and parental stress (QRS-F:  $r = -.358$ ,  $p < .01$ ), HADS anxiety ( $r = -.322$ ,  $p < .01$ ) and HADS depression ( $r = -.281$ ,  $p < .01$ ). In particular, there were significant associations linking parental stress to parental perception of deterioration in mobility/walking skills ( $r = -.301$ ,  $p < .005$ ), mood changes ( $r = -.229$ ,  $p < .05$ ) and problems with anxiety ( $r = -.363$ ,  $p < .005$ ). Increased parental anxiety was correlated with parental perception of deterioration in mobility/walking skills ( $r = -.312$ ,  $p < .005$ ) purposeful hands use ( $r = -.260$ ,  $p < .05$ ), mood changes ( $r = -.250$ ,  $p < .05$ ) and problems with anxiety ( $r = -.335$ ,  $p < .005$ ). Significant associations were also found between increased parental depression and perception of deterioration of mobility/walking ( $r = -.320$ ,  $p < .005$ ), purposeful hand use ( $r = -.213$ ,  $p < .05$ ), increased body rocking ( $r = -.227$ ,  $p < .05$ ) and problems with anxiety ( $r = -.301$ ,  $p < .005$ )

Positive gain (as measured with the PGS) was significantly associated with parental perception of improvement in general physical fitness ( $r = .227$ ,  $p < .05$ ), purposeful hand use ( $r = .212$ ,  $p < .05$ ) and mood changes ( $r = .217$ ,  $p < .05$ ).

Analyses revealed significant association between positive affect (as measured by the PAS) and parental perception of improvement in physical fitness ( $r = .2191$ ,  $p < .05$ ), mobility/walking ( $r = .264$ ,  $p < .05$ ), purposeful hand use ( $r = .283$ ,  $p < .01$ ), mood changes ( $r = .223$ ,  $p < .05$ ) and problems with anxiety ( $r = -.323$ ,  $p < .005$ ).

## 9.5 Discussion

This chapter explored the psychological well-being of a group of 80 parents with a daughter diagnosed with RTT living at home. There were too few fathers for meaningful comparison with mothers but, to the extent that there were data, they agreed with the literature that indicates that mothers generally experience more stress, anxiety and depression symptoms than fathers (Olsson and Hwang 2001), findings that are generally associated with caregiving difficulties (Roach et al. 1999).

The findings from this study indicated that younger parents experienced a higher level of stress. Results of previous studies of the relationship between parental age and parental stress are contradictory. Cook et al. (1994) reported that older parents experienced less stress overall than younger parents, but they reported that they experienced a greater level of emotional and cognitive stress. Hwa Ha et al. (2008) reported that negative affect and poor well-being attenuate with parental age. Studies of the effects of child characteristics on parental stress and well-being have rarely included parents at different stages of their life. The adaptation model (Lazarus and Folkman 1984) suggests parents adapt to the challenges and stressors of having a child with disability over time. In contrast, the cumulative model suggests that the more the parents are exposed to challenges and stress the more they will become vulnerable to chronic stress over time. Results from this study suggests that older parents tend to adapt and stress attenuates. However, this result must be interpreted with caution as other variables such as the availability of support and workings of the support system need to be explored. Furthermore, this is a cross-sectional analysis and it is not known how the current level of stress, anxiety and depression experienced by older parents compares with that which they experienced in the past

when they were younger.

Other studies of this population have found that parents of children with RTT experience a high level of stress and mental and physical ill-health (Laurvick et al. 2005; Perry et al. 1992). However, in general, parents with a child/adult with RTT in this study reported relatively moderate stress and high levels of positive gain and affect. Griffith et al. (2011) reported higher levels of stress, anxiety and depression than those found here among three different syndromes (Angelman, Cornelia de Lange and Cri du Chat syndrome). In addition, the study revealed that parents with a child with Angelman syndrome reported higher levels of stress compared to parents of children with Cornelia de Lange and Cri du Chat syndromes. Moreover, compared to Griffith et al. (2011) who reported mean scores of 6.9, 5.7 and 7.4 on the Positive Gains Scale and mean scores of 18.6, 21.5 and 19.1 on the Positive Affect Scale for mothers of offspring with Angelman, Cornelia de Lange and Cri du Chat syndromes respectively, parents with a child with RTT reported more positive gains and affect (mean = 4.7 and 35.1 for PGS and PAS respectively). In the Griffith et al. (2011) study, the authors only included those children who displayed self-injurious and aggressive behaviour daily so differences may be related to the challenging behaviours displayed by the children.

Interestingly, severity of the clinical phenotype was not associated with family psychological well-being. These results are consistent with the findings of other studies that have found no relationship between the clinical severity and functional skills of the child and maternal physical and mental health (Laurvick et al. 2005; King et al. 1999; Manuel et al. 2003). Increased parental stress, anxiety and depression were associated with the behavioural presentation of the RTT child. These findings are consistent with Laurvick et al. (2005), who reported that mothers'

mental health score increased (indicating better mental health) as the RSBQ score decreased. In particular, the association found here was evident for subscales relating to mood, fear/anxiety, body rocking and expressionless face. In addition, the absence of facial movements such as mouth/face grimacing and repetitive tongue movements was linked to better maternal mental health. Alternative hypotheses for this association are that the presence of these repetitive/grimacing movements are associated with the neurological severity of the condition or that mothers may see these behaviours as socially unacceptable and thus be embarrassed.

Several other studies have reported an association between severity of the child's behavioural problems and parental mental health (Baker et al. 2003; Eisenhower et al. 2009; McDonald et al. 1999; Raina et al. 2005; Schieve et al. 2006; Waddington et al. 1992). In a study exploring the well-being of parents with a child with cerebral palsy, Raina et al. (2005) found a strong association between child behaviour and parental well-being. In particular, severity of behavioural problems was associated with worse psychological and physical health of parents. Additionally, stress among parents of children with Cornelia de Lange syndrome was associated with child behavioural problems (Wulffaert et al. 2009).

Parents in this study reported a relatively high level of positive gain and affect compared to those of offspring with other syndromes. Using a matched group design, Griffiths et al. (2010) examined maternal well-being of a group of children with a diagnosis of Down syndrome and autism. The results revealed that mothers of children with autism reported a lower positive contribution (such as happiness, closeness of the family) than mothers with children with Down syndrome and mixed aetiology of ID. However, there was no association between positive gain or affect and behavioural and clinical severity found here, except for the relationship between

less positive affect and scoliosis. However, findings from this study indicate that mothers experiencing high levels of stress, anxiety and depression were less likely to report positive feelings and mothers experiencing high levels of stress were less likely to report positive gains.

This is the first study to explore parental perceptions of progression and regression of behavioural and clinical presentation in this population. Both the balance of overall parental perception and perception of deterioration in specific areas were associated with parental stress, anxiety and depression. In addition, parents who perceived progression of skills reported greater positive gains and affect, particularly in relation to improvement in mobility, general physical fitness, anxiety and mood changes.

Research has suggested that positive impact of the child member can occur concurrently with negative impact. In this study, parents who reported high positive gains and affect tended to have low levels of stress, anxiety and depression. These findings may sustain the hypothesis of an adaptation process involving positive perceptions and feelings. However, this model needs further testing. Further studies should explore the role of other variables (i.e. social support systems, coping strategies, work and social life, socio-economic status) and the psychological processes that lead to positive and negative perceptions.

**CHAPTER 10**  
**A LONGITUDINAL STUDY OF BEHAVIOURAL FEATURES OF 50**  
**FEMALES WITH RETT SYNDROME**

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**10.1 Introduction**

Data from the cross-sectional survey of this study indicated that children below the age of 12 consistently scored higher than the other groups in clinical and behavioural variables, indicating that level of activity and mood decreased with age. Moreover, although the results of statistical testing were not significant, there was a consistent decrease in scores during adolescence (12-17 years old) and adulthood (18-25 years and 26 years and older). These results give some indications of the developmental changes in behavioural and emotional presentation in RTT that may occur as the child enters adolescence and adulthood. However these results need to be interpreted with some cautions as a cross sectional methodology was used to analyse the data.

In the last decade advances in genetic and neurobiological understanding has led to new discoveries of the molecular mechanism underpinning RTT. More recently there has been an increase in studies attempting to understand the association between the genotype and clinical and behavioural characteristics. However, very few studies have included a developmental approach to understand the atypical development in RTT.

Very little is known about developmental change in behavioural and emotional characteristics in individuals with RTT.

Data from the literature review revealed a general lack of longitudinal studies. Only two studies were in fact identified that analysed behavioural features of the syndrome over time. Woodyatt and Ozanne (1993) analysed the communication skills of 6 girls

with RTT over 3 years period. They found that the skills remained at the pre-intentional level, albeit that 5 of the 6 girls showed some improvement in social skills. Young and colleagues (2007) examined sleep disturbances in a large group of females with RTT and reported higher frequencies of sleep disturbances in the younger group compared to older females. A further study (not included in the literature review) investigated hand function longitudinally at 3 time points. They found that level of hand function, motor skills and age at baseline were predictors of skill levels at follow up. Women aged 19 and over and individuals who were unable to walk and feed at baseline were more likely to have lost hand function in the 3-4 years follow up period. These findings were consistent with a previous study in which Downs et al. (2010) indicated that individuals aged 19 years and over had the lowest level of functional hand skills.

Several examples of developmental change in other syndromes can be found in the literature. Studies of behavioural and emotional development in individuals with Fragile X syndrome have indicated a steady improvement in behavioural and emotional disturbances, with a decline in disruptive behaviour over time but an increase in antisocial behaviour (Einfeld et al. 1999) and an increase in ASD traits and social avoidance with age (Hatton et al. 2006). Studies on the behavioural and cognitive phenotype of William syndrome indicated that there is a decrease in emotional and behavioural problems over time. An increase risk of developing dementia in Down syndrome (Holland et al. 1998) and an increase incidence of developing schizophrenia in adults with 22q11 deletion syndrome (Bassett et al. 2005) are other examples of age-related change that have a significant impact on the life of the individuals. Self-injurious behaviour and social anxiety has been reported to increase with age in individuals with Cornelia de Lange syndrome (Berney et al. 1999; Basile et al. 2007; Kilne et al. 2007; Oliver et al. 2010). In addition, recent studies on the behavioural phenotype of

Angelman syndrome have reported that the smiling and laughing typical of the syndrome tend to decrease with age (Horsley and Oliver 2006).

The aim of this study was to follow up the initial sample with RTT gained here to examine potential changes in behavioural presentation over 16 months in Overactivity, Impulsivity, Mood, Interest/Pleasure, RTT behavioural presentation (RSBQ) and presence of self- injurious behaviours. Moreover, change over time in family psychological well-being was also assessed. The interval between the initial sample and the follow-up was necessarily constrained by the overall length of study that could be undertaken. The two data collections were separated by 16 months.

## **10.2 Recruitment and measures**

The majority of participants in the initial sample were invited to take part in the follow up survey. The aim was to follow up this sample 16 months after the first data collection. Questionnaires were, therefore, distributed at different times depending on when the initial survey questionnaire was returned. Distribution of follow-up questionnaires commenced on March 2011 and ended in August 2011. A total of 72 questionnaires were distributed to families. Fifty families (69.4%) returned a completed questionnaire.

An invitation letter, containing an information leaflet, a consent form, prepaid envelope and prepaid card that families could return if they did not wish to take part in the second part of the study was sent to the selected families. Families were asked again to complete a set of two questionnaire packs containing 9 informant-based scales related to the child/adult behaviour with RTT and 11 scales related to the family psychological

well-being (see *Appendixes C – 2 and C – 3 for a copy of the information leaflet, consent forms and questionnaire packs*).

The Repetitive Behaviour Questionnaire (RBQ) and Developmental Behaviour Checklist (DBC) were not included in the longitudinal survey and the Vineland Adaptive Behavior Scale (VABS) was not administered again. Participant scores had initially been very low on all three measures and it was not deemed suitable to re-administer the assessments again after so short a time. Unlike the first data collection, the questionnaire pack related to family well-being did not include information about the support groups with whom the families had contact. However, a question regarding employment was added. (See paragraphs 5.5.1- 5.5.2 for information about the measures and psychometric properties).

### **10.3 Data analysis**

#### *10.3.1 Missing data*

A similar procedure to that used for the part one survey was followed. However, parents could not be asked to answer missing questions as the telephone contact to undertake the VABS was not part of the follow-up. After checking for missing data, 1 case was excluded from the analysis of the MIPQ (33.3% of data missing), RSBQ (46.7% of missing data) and QRS (20% of missing data). A further case had 7.2% of data missing (1 question). This was substituted with the mean score for the sub-scale.

#### *10.3.2 Normality tests*

All data were tested for normality using a Kolmogorov-Smirnov test and a critical region of  $p < .05$ . Results of such tests were non significant for some of the sub-scales

(RSBQ total score and fear/anxiety sub-scale; HADS anxiety and PAS), indicating that the data were normally distributed. However, data for other subscales/measures were non-normal (RSBQ; AQ total and sub-scales, MIPQ mood, Interest & Pleasure sub-scales; QRS, PGS, HADS depression). Hence, Wilcoxon rank-sum tests were used for all analyses. (See *Appendix G – Longitudinal data normality tests for tests analyses and histograms*).

### 10.3.3 Analysis

The analysis focused on establishing longitudinal relationships between changes in RTT and family adjustment. The first part describes demographic characteristics and clinical features of the sample with RTT at Time 2 and explores change in clinical features between Time 1 and Time 2. The second part explores change over time in the behavioural presentation of individuals. Effect sizes were calculated where significant differences were revealed using the following formula:

$$r = \frac{z}{\sqrt{N}}$$

where  $r$  is the estimated effect size,  $z$  is the  $z$  score and  $N$  the number of participants (Field 2009). The third part focused on exploring change in family variables between Time 1 and Time 2. Correlation between family variables and RTT behavioural presentation was also explored at Time 2.

## 10.4 RTT sample demographic characteristics

The age of the RTT sample at Time 2 ranged from 7 years to 48 years with a mean of 22.9 years. Seventy-six percent of the sample was diagnosed with Classic RTT, the remainder with Atypical (20.0%) and *MECP2* disorder (4.0%). The majority (84%) had

a confirmed mutation in the *MECP2* gene. The other 16.0% had either not been tested (10.0%) or the mutation was not known (6.0%). Most common single mutations included: T158M (2), R168X (5), R255X (4), R306c (3), R294X (2), R270X (3), C-terminal (9), R133C (1) and R106W (1). Age of regression was between 7 and 48 months, with a mean age of 18 months.

#### 10.4.1 Skills and characteristic RTT features at Time 2

Clinical features, current abilities and health status of the RTT sample at Time 2 were explored and compared to Time 1. Table 10.1 presents data on the follow-up sample's current abilities at Time 2 with comparison to those at Time 1 and associated test statistics.

**Table 10.1 Percentages of individuals possessing selected abilities at Time 1 and Time 2**

	<b>Time 2</b>	<b>Time 1</b>	<b>z</b>	<b>p</b>
Concentrate	86.0% (43)	90.0 % (45)	-.302	.763
Hold objects	42.0% (21)	38.0 % (19)	-1.000	.317
Reach for objects	54.0 % (27)	56.0 % (28)	-.302	.763
Sit unsupported	56.0 % (28)	64.0 % (32)	-.302	.763
Walk with support	42.0 % (21)	50.0 % (25)	.000	1.000
Walk unsupported	34.0 % (17)	40.0 % (20)	.000	1.000
Feeding with fingers	32.0 % (16)	36.0 % (18)	.000	1.000
Feed using spoon/fork	20.0 % (10)	24.0 % (12)	-.447	.655
Communicate with gestures/sounds	62.0 % (31)	66.0 % (33)	-.749	.454
Speak/sign	18.0 % (9)	14.0 % (7)	-1.000	.317
Make choices	80.0 % (40)	74.0 % (37)	.000	1.000

By Time 2, a few individuals had lost some motor skills, such as sitting, walking and feeding compared to Time 1 and a few others had gained some skills in areas such as holding objects, making choices and ability to communicate. Wilcoxon Signed Ranks tests indicated that there were no significant changes over time in the sample.

#### *10.4.2.1 Health problems over time*

Mean health problems score in the previous month at Time 2 was 4.70 compared to 4.02 at Time 1. Analysis indicated a significant change over 16 months in the health of the sample with increasing health problems reported ( $z = -2.303$ ,  $p < .05$ ,  $r = -0.23$ ).

Health problems in the previous month most commonly reported at Time 2 were: dental problems (18/50), gastrointestinal problems (31/50), bowel problems (24/50) and epilepsy (27/50). Analysis revealed a significant difference between Time 1 and Time 2 in dental problems ( $z = -2.707$ ,  $p < .05$ ,  $r = -0.27$ ) and gastro-intestinal problems ( $z = -2.399$ ,  $p < .05$ ,  $r = -0.23$ ), indicating that dental and gastro-intestinal problems increased between Time 1 and Time 2.

#### **10.4.2 Changes in behavioural presentation**

No significant changes were found in the RSBQ between Time 1 and Time 2. All girls included in the longitudinal study were reported to have repetitive hand stereotypies at both time points. 14 (28%) of the 50 individuals included in the longitudinal study displayed self-injurious behaviour at Time 1. At Time 2, 14 (28.0%) were reported still to display self-injurious behaviour. There was no change in the occurrence or severity of self-injurious behaviour over time ( $z = -.447$ ,  $p > .05$ ).

Significant differences over time were found in the AQ total score (from 14.26 at Time 1 to 15.88 at Time 2,  $z = -2.045$ ,  $p < .05$ ,  $r = -0.20$ ) and MIPQ - S total score (from 33.63 at Time 1 to 30.9 at Time 2,  $z = -2.957$ ,  $p < .005$ ,  $r = -0.29$ ). Tables 10.2 – 10.5 show means (SDs), ranges and test statistics for the four age groups at Time 1 and Time 2 for the AQ total score and the MIPQ – S total score.

**Table 10.4 Mean score (SD), range and statistical analyses on AQ total score and MIPQ - S subscales for the children group (<12 years old)**

	<b>Time 1</b>	<b>Time 2</b>	<b>z</b>	<b>p</b>
AQ Total	19.37 (13.02) 5 – 43	23.75 (12.39) 7 – 40	- 1.680	.093
MIPQ – S Total	36.42 (6.02) 26 – 44	34.50 (6.39) 22 – 44	- 0.912	.362

**Table 10.5 Mean score (SD), range and statistical analyses on the AQ total score, MIPQ - S subscales for the adolescent group (12 - 17 years old)**

	<b>Time 1</b>	<b>Time 2</b>	<b>z</b>	<b>p</b>
AQ Total	13.60 (12.65) 1 – 36.50	13.25 (7.36) 4 – 28	- 1.429	.153
MIPQ – S total	32.08 (4.69) 22 – 38	29.66 (4.94) 22 – 35	-2.018	.044*

\* $r = - 0.20$

**Table 10.6 Mean scores (SD), range and statistical analyses on the AQ total score, MIPQ - S subscales for the young adult group (18 - 25 years old)**

	<b>Time 1</b>	<b>Time 2</b>	<b>z</b>	<b>p</b>
AQ Total	13.69 (14.29) 0 – 44	16.46 (16.28) 0 – 52	-1.871	.061
MIPQ – S Total	34.00 (4.89) 28 – 40	32.46 (6.77) 19 – 46	-1.061	.289

**Table 10.7 Mean scores (SD), range and statistical analyses on the AQ total scores, MIPQ - S subscales for the adult group (26 years and older)**

	<b>Time 1</b>	<b>Time 2</b>	<b>z</b>	<b>p</b>
AQ Total	12.59 (9.62) 0 – 40	13.58 (7.45) 0 – 35	- .700	.484
MIPQ – S Total	32.68 (5.61) 19 – 39	28.88 (5.25) 13 – 37	-1.815	.070

There was a tendency for the AQ total for each age group to increase over time and for the MIPQ - S total to reduce over time. However, changes were not significant apart from the reduction in mood for the adolescent group (12-17 years old). Even here, the effect size was small ( $r = - 0.20$ ).

*10.4.2.1 Association between severity of the clinical phenotype and change in activity level and mood over time*

Changes over time in the AQ and MIPQ- S were analysed separately for those with a mild ( $\leq 9$ ) or severe ( $>9$ ) clinical severity score (see Tables 10.6 and 10.7). Individuals with a severe clinical phenotype showed a significant increase in the AQ total score and a significant decrease in the MIPQ – S total score, both with a moderate effect size ( $r = - 0.38$ ). No significant change over time was found in the AQ or MIPQ-S subscales for either group.

**Table 10.8 Mean scores (SD), range and statistical analyses between clinical severity groups (Mild/Severe) at Time 1 and Time 2 for the AQ total and subscales.**

		Time 1	Time 2	z	p
AQ Total	Mild	19.37 (12.15) 1 – 44	20.38 (11.75) 6 – 52	-.899	.369
	Severe	5.47 (4.98) 0 – 20	8.52 (5.82) 0 – 16	-2.360	.018*
Overactivity	Mild	10.45 (5.96) 0 – 25	11.06 (6.43) 3 – 26	-.774	.439
	Severe	4.73 (3.24) 0 – 11	4.43 (3.40) 0 – 10	-.442	.658
Impulsivity (Mobile)	Mild	10.00 (6.50) 2 – 22	9.54 (6.17) 1 – 22	-.329	.742
	Severe	/	/	/	/
Impulsivity (Immobile)	Mild	5.43 (10.13) 0 – 24	3.14 (4.28) 0 – 10.50	-1.069	.285
	Severe	0.75 (2.31) 0 – 9	1.68 (2.22) 0 – 6	-1.612	.107
Impulsivity (All)	Mild	8.82 (7.69) 0 – 24	7.93 (6.30) 0 – 22	-.338	.736
	Severe	0.75 (2.31) 0 – 9	1.68 (2.22) 0 – 6	-1.612	.107

\*r = - 0.38

**Table 10.9 Mean (SD), Range and statistics test at Time 1 and Time 2 between severity scores groups (Mild/Severe) of the MIPQ - S subscales.**

		Time 1	Time 2	z	p
MIPQ – S Total	Mild	34.09 (5.64) 22 – 44	32.06 (6.19) 19 – 46	-1.887	.059
	Severe	32.83 (5.06) 19 – 39	29.00 (5.31) 13 – 37	-2.349	.019*
MIPQ – S Mood sub-scale	Mild	18.64 (2.51) 12 – 23	18.67 (3.62) 10 – 24	-.419	.675
	Severe	19.05 (2.94) 12 – 22	18.22 (2.23) 14 – 21	-1.286	.198
MIPQ – S Interest & pleasure	Mild	15.45 (3.65) 10 – 23	15.06 (3.28) 10 – 23	-.642	.521
	Severe	13.77 (3.15) 8 – 19	13.44 (2.68) 9 – 18	-.400	.689

\*r = - 0.38

## **10.5 Part two: A longitudinal study of psychological well-being of families with a daughter with Rett syndrome**

### **10.5.1 Introduction**

The second part of this chapter describes the psychological well-being of families with a daughter with RTT over time, the first longitudinal study to my knowledge to do so. Data from the cross sectional analysis at Time 1 indicated that the severity of behavioural presentation (as measured with the RSBQ) was associated with family stress, anxiety and depression, rather than the clinical severity of the phenotype (for a discussion of the literature on family psychological well-being see Chapter 9). In particular parental stress (QRS – F scores) was related to the RSBQ Total, General Mood and Fear /Anxiety subscales scores. Parental anxiety (HADS) was related to the RSBQ Total and the General Mood, Repetitive Face Movements and Fear / Anxiety subscales. Parental Depression (HADS) was related to the RSBQ Total and the General Mood and Body Rocking and Expressionless Face subscales. In addition, an inverse relationship was found between the levels of stress, anxiety and depression parents reported and their positive experiences and feelings. Moreover, associations between parental perception of progression or regression of skills and behaviour were found that linked parental stress to deterioration in mobility skills, mood changes and increased problems with anxiety.

The literature on the relationship between severity of child behavioural presentation and family well-being is limited. There are few longitudinal studies exploring the association between child behavioural problems and parental well-being in the intellectual disability literature as a whole. Findings from previous studies support the hypothesis of a bidirectional relationship between parental stress and increased

frequency/severity of behavioural problems (Hastings et al. 2006). Hastings and colleagues (2006) found evidence of a casual relationship between child behavioural problems and parental distress over time. In addition, maternal depression at Time 1 was a predictor of increased depression over time. Other studies have also reported evidence of an association between maternal well-being and child behavioural problems (Baker et al. 2003, Lecavalier et al. 2006). Baker et al. (2003) measured child behavioural problems and parenting stress at two time points (36 months and 48 months). They found that changes in child behaviour over one year period were associated with increased parental stress.

### **10.5.2 Aims of the study**

The aim of this study was to explore the progression of psychological well-being of families with a daughter with RTT over a 16 month period. Analysis includes only families with a daughter living at home (N=40) and explored:

- 1) Levels of stress, anxiety, depression and positive experiences and feelings at Time 2 compared to Time 1.
- 2) The relationship between child characteristics (age, severity score, RSBQ) and family stress, anxiety, depression, positive experiences and feelings at Time 2.
- 3) The extent to which child behavioural presentation predicted increased parenting stress, anxiety and depression.
- 4) The association between parental perception of progression/regression of behavioural and clinical symptoms and family positive and negative experiences over time.

### 10.5.3 Demographics characteristics of the families

Ten of the 50 families that returned the follow up questionnaire were excluded from the analysis of family measures because their daughters were living in accommodation other than the family home. All parents completing the questionnaire were mothers (biological mothers: 92.5%; foster mother: 5.0%; adoptive mother 2.5%). Twenty-nine (72.5%) of participants were married. Ten percent of mothers were reported to work full time. The majority worked part-time (42.5%), and the remainder were either not working (30.0%) or retired (17.5%). Seventeen (42.5%) of mothers reported that they gave up work to care for their daughter with RTT.

### 10.5.4 Stress, anxiety, depression and positive outcomes

Table 10.8 summarises mean scores of the QRS –F, HADS Anxiety, HADS Depression, PGS and PAS at Time 2 and Time 1 for the 40 families included in the longitudinal analysis. Change in the QRS – F Stress over time was significant ( $z = -2.334$ ,  $p < .05$ ), indicating an increase in family stress over the 16 months period. Change over time in the other family measures (HADS anxiety and depression, PGS, PAS) was not.

**Table 10.8 Mean (SD) and range of the family scales at Time 1 and Time 2**

		QRS – F Stress	HADS Anxiety	HADS Depression	PGS	PAS
Mean (SD)	Time 1	6.80 (3.32)	7.55 (3.41)	4.60 (2.86)	5.17 (4.41)	34.45 (7.40)
		0 – 13	0 – 14	0 – 11	0 – 18	16 – 47
Range	Time 2	7.77 (3.21)	8.12 (3.33)	4.95 (3.41)	6.55 (5.63)	35.12 (7.49)
		0 – 14	0 – 14	0 – 12	0 – 27	16 – 50

Stability in maternal stress, anxiety, depression and positive outcomes and feelings was explored by correlating Time 1 and Time 2 scores. This indicated a moderate stability for all of the family measures (QRS-F:  $r = 0.66$ ; HADS Anxiety:  $r = 0.65$ ; HADS Depression:  $r = 0.67$ ; PGS:  $r = 0.56$ ; PAS:  $r = 0.69$ )<sup>10</sup>.

Correlation analyses (see Table 10.9) did not reveal any significant associations between the ages of the children and the family measures. In terms of clinical severity scores, there was an inverse correlation between the epilepsy domain of the severity score and the PGS score and a positive association between the scoliosis domain of the severity score and HADS Anxiety.

**Table 10.9 Correlation analyses of family measures, child age and clinical severity**

	QRS – F stress	HADS Anxiety	HADS Depression	PGS	PAS
Child's age	.074	.033	.035	.218	.205
Severity score Total	.054	.234	.025	-.250	.201
Sitting	.207	.288	.075	-.244	-.199
Walking	.056	-.037	-.215	-.296	-.074
Hand use	-.212	.110	.096	-.109	-.108
Speech	-.080	.094	.005	-.160	-.191
Epilepsy	.076	.068	-.076	-.340*	-.100
Scoliosis	.086	.363*	.220	.021	-.171

\*  $p < .05$

As at T1, severity of behavioural presentation of the person with RTT (i.e., RSBQ) was found to be associated with family problems. In particular, family stress (QRS – F) was related to RSBQ Fear/Anxiety; parental anxiety (HADS) was related to RSBQ total, General mood, Breathing problems, Repetitive face movements, Fear/Anxiety and

<sup>10</sup> All significant at  $p < .001$  value

parental depression (HADS) was related to RSBQ General mood and Fear/Anxiety (See Table 10.10).

**Table 10.10 Correlation coefficients for behavioural presentation of the RTT person and family measures**

	QRS – F stress	HADS Anxiety	HADS Depression	PGS	PAS
RSBQ total	.105	.456***	.313(.050)	-.112	-.271
General Mood	.094	.529***	.353*	-.040	-.271
Breathing problems	.225	.460***	.224	-.248	-.189
Hands behaviour	.027	.211	.108	.035	-.019
Repetitive face movements	.020	.444**	.253	-.061	-.107
Body rocking and expressionless face	-.179	.203	.142	-.117	.033
Night-time	-.174	.190	.138	.234	-.223
Fear/Anxiety	.328*	.460***	.412**	-.158	-.305
Walking/standing	-.103	-.119	.070	.195	.105

\*p< .05, \*\* p< .01 \*\*\*p< .005

The longitudinal relationship between maternal stress, anxiety and depression and child behavioural presentation were explored further using regression analysis to test the hypothesis that severity of child behavioural presentation predicts increased parental stress, anxiety and depression. For this analysis, only the variables that were significantly associated with family measures at Time 1 (QRS-F, HADS Anxiety and Depression) were used.

Following the model used in other studies (Baker et al. 2003; Hastings et al. 2006; Lecavalier et al. 2006), three sets of analyses were conducted. In the first analysis, the QRS-F Time 2 score was entered as the dependent variable and on step 1 the QRS-F Time 1 score was entered. On step 2, the RSBQ total score at Time 1 was entered together with the change in RSBQ scores between T1 and T2 (derived by subtracting scores at T1 from scores at T2).

Table 10.11 and 10.12 summaries regression analyses for QRS and RSBQ.

**Table 10.11 Regression analysis for maternal stress (QRS) at Time 2**

Predictor	Beta	P
QRS Time 1	0.687	0.000

$R^2 = 0.47$ , adjusted  $R^2 = 0.46$ ,  $F_{1,38} = 34.01$ ,  $P = 0.000$

**Table 10.12 Regression analysis for QRS and RSBQ**

	Predictor	Beta	P
Blocks 1 & 2	QRS at Time 1	0.691	0.000
	RSBQ at Time 1	0.075	0.548
	RSBQ change (Time 2- Time 1)	0.073	0.557

$R^2 = 0.48$ , adjusted  $R^2 = 0.44$ ,  $F_{3,36} = 11.14$ ,  $P = 0.000$ , change in  $R^2 = 0.01$  change in  $F_{2,36} = 0.31$ ,  $P = 0.733$

This model indicated that there was a significant change in maternal stress over time (QRS - baseline QRS predicts follow-up QRS) but RSBQ at Time 1 and change in RSBQ did not add significantly to explanation.

In the second and third analyses, the Time 2 scores of the HADS Anxiety and HADS Depression were entered as the dependent variables and the Time 1 scores of the HADS Anxiety and HADS Depression as independent variables. Tables 10.13-10.16 summarise results from the regression analyses.

**Table 10.13 Regression analysis for HADS Anxiety at Time 2**

	<b>Predictors</b>	<b>Beta</b>	<b>P</b>
Block 1	HADS Anxiety at Time 1	0.698	0.000

$R^2 = 0.49$ , adjusted  $R^2 = 0.47$ ,  $F_{1,37} = 35.10$ ,  $P = 0.000$

**Table 10.14 Regression analysis for HADS Anxiety and RSBQ**

	<b>Predictors</b>	<b>Beta</b>	<b>P</b>
Block 1 & 2	HADS Anxiety at Time 1	0.589	0.000
	RSBQ at Time 1	0.272	0.053
	RSBQ change (Time 2-Time 1)	0.198	0.093

$R^2 = 0.57$ , adjusted  $R^2 = 0.53$ ,  $F_{3,35} = 15.44$ ,  $P = 0.000$ , change in  $R^2 = 0.08$  change in  $F_{2,35} = 3.37$ ,  $P = 0.046$

Results from this analysis indicated that HADS Anxiety at Time 1 predicts follow-up HADS Anxiety scores. However as from previous analysis, RSBQ scores at Time 1 and change in RSBQ add marginally to explanation (i.e., change in  $R^2$  from adding Block 2 is significant but neither of the beta coefficients for the two RSBQ variables is).

**Table 10.15 Regression analysis of HADS Depression at Time 2**

	<b>Predictor</b>	<b>Beta</b>	<b>P</b>
Block 1	HADS Depression at Time 1	0.678	0.000

$R^2 = 0.46$ , adjusted  $R^2 = 0.45$ ,  $F_{1,38} = 32.31$ ,  $P = 0.000$

**Table 10.16 Regression analysis for HADS Depression at Time 2 and RSBQ**

	<b>Predictor</b>	<b>Beta</b>	<b>P</b>
Block 1 & 2	HADS Depression at Time 1	0.641	0.000
	RSBQ at Time 1	0.172	0.176
	RSBQ change (Time 2-Time 1)	0.156	0.200

$R^2 = 0.50$ , adjusted  $R^2 = 0.46$ ,  $F_{3,36} = 12.14$ ,  $P = 0.000$ , change in  $R^2 = 0.04$  change in  $F_{2,36} = 1.57$ ,  $P = 0.222$

Table 10.15-10.16 show results from the third regression analysis. Level of maternal depression at Time 1 was a significant predictor of level of depression at Time 2. However RSBQ scores and changes in RSBQ scores did not predictor increased maternal depression.

### **10.5.5 Parental perception of regression/progression of skills**

The distribution of parental perception of regression/progression of skills at Time 2 was similar to that at Time 1. Most parents considered the condition of the daughter to be static. Mean total score (see paragraph 5.5.2.7 for scoring procedure) was  $-0.35$  (SD 4.11, Range -10 to 8). A Wilcoxon signed rank test did not reveal a significant change in parental perception over time ( $z = -.215, p > .05$ ). Correlation analyses were conducted to explore the relationship between parental perception of regression/progression of skills at Time 2 and family psychological well-being at Time 2. Stress and anxiety were associated with perceived worsening of repetitive hand movements and problems with anxiety (see Table 10.12). Depression was associated with perceived worsening of physical robustness/fitness and mood changes. Positive feelings were associated with reduced breathing abnormalities and problems with anxiety and improved purposeful hand use.

**Table 10.17 Correlation coefficients of RSBQ and parental perception of regression/progression**

<b>Domains</b>	<b>QRS-F Stress</b>	<b>HADS Anxiety</b>	<b>HADS Depression</b>	<b>PGS</b>	<b>PAS</b>
Breathing abnormalities	-.270	-.216	-.198	-.057	.316*
Physical robustness/fitness	-.120	-.239	-.375*	.258	.331*
Mobility/walking	-.126	-.039	-.033	-.037	.096
Communication	-.109	-.188	-.067	.195	.127
Purposeful hand use	-.208	-.291	-.238	-.041	.340*
Repetitive hand movements	-.330*	-.434**	-.095	-.235	.203
Body rocking	.076	-.426**	-.224	-.293	.122
Mood changes	-.312	-.315	-.324*	.047	.359*
Problems with anxiety	-.475**	-.464**	-.360*	-.041	.471**
Night-time behaviours	-.075	-.107	-.208	.125	.166
Feeding problems	-.064	-.009	-.151	-.106	.019

\*p< .05; \*\*p< .005

## 10.6 Discussion

In this chapter data of the longitudinal study was analysed. This is one of the first study to explore developmental changes in Rett syndrome behavioural characteristics, mood and activity level using a longitudinal methodology. The aim of this study was to explore how Rett syndrome behavioural features, level of mood, interest and pleasure, impulsivity and overactivity changed over 16 months period in a group of females with RTT. In addition, the study analysed how family negative and positive experiences change over time and whether changes in behavioural features influence parental level of stress, anxiety and depression over time.

In the first part clinical and behavioural features of a group of 50 females with RTT was analysed and differences between Time 1 and Time 2 was explored.

In the second part, family adjustment and psychological well-being over time was explored. The aim of this part of the study was to explored changes over time in the behavioural presentation of females with RTT and whether changes in behavioural presentation influence family stress, anxiety and depression. No other studies reported

longitudinal data on the well-being family of females with RTT, this study reported novel data.

Data from the longitudinal study suggested that participants' clinical and behavioural features remain stable over time with only few exceptions. No changes were found in areas such as motor, sitting and holding objects. Few participants were reported to have lost some skills in motor, sitting and feeding abilities and some to have re-gained some skills in communication and holding objects, however statistical analysis did not reveal any significant changes over time. Health problems increased over time, in particular gastro-intestinal and dental problems.

Gastrointestinal problems are common in RTT and include: feeding problems, swallowing problems, gastro-esophageal reflux, constipation and failure to thrive. Motil et al. (1999) reported gastrointestinal dysmotility in 92% of the sample. They also reported that problems such as gastro-esophageal reflux, vomiting, night-time waking were less likely to occur with increased age. Moreover, Vignoli et al. (2012) reported an improvement in gastroesophageal reflux over time. Data from studies of other genetic syndromes reported gastro-intestinal problems in individuals with Cornelia de Lange syndrome, with an occurrence of 65% (Luzzani et al. 2003). A recent study (Holbach et al. 2012), reported longitudinal data of a group of 37 females with RTT aged 21 years over 5 years. The results of the study reported improvements in areas such as general health, cognitive and communication skills, autonomic problems (i.e. sleep disturbances, and breathing abnormalities) and decrease in epilepsy. However increase in motor and night screaming was reported.

In the first part of the longitudinal study, differences across age groups at Time 2 was explored by repeating the analysis carried out in the cross-sectional study and although analysis did not revealed any differences across the age groups, a more fine grained analysis indicated that children below the age of 12 years had higher scores in Overactivity and Impulsivity compared to adult (above 26 years). It is worth noting that although statistical analysis revealed few significant differences across the age groups, there was a consistent pattern in the data which suggested that in older females behavioural features tend to decrease with age. Of particular interest the pattern of the data from the MIPQ-S indicated that mood, interest and pleasure decrease with age. However caution must be taken when interpreting these results due to the small number of participants in each group and the study had a follow up of only 16 months. Thus further research employing a large cohort and a longer follow up period would give more robust results. In addition this study did not explore associations with health problems. There is evidence in the literature that suggests that health problems, such as gastro-esophageal reflux are associated with behavioural problems. Berg et al. (2007) reported an association between low affect and health problems in individuals with Cornelia de Lange syndrome.

There was evidence in the longitudinal analysis that health problems, in particular gastrointestinal and dental problem increase over time thus it is important to investigate in further study a link between increased health problems and increased level of overactivity and impulsivity and decreased in mood and interest and pleasure.

Longitudinal analysis did not show any changes in Rett syndrome behavioural features, mood, interest and pleasure, overactivity and impulsivity over 16 months period. The only differences observed were in the total score of the AQ and MIPQ-S

indicating a decrease in mood and interest and pleasure and an increase in activity level. However when effects size was explored this was found to be small. A more detailed analysis revealed that the adolescence group experienced a decreased in level of mood over a period of 16 months.

In this study an increase in activity and decrease in mood was found in participants with a more severe phenotype. One explanation of this effect could be linked to the fact that cases with a more severe phenotype do not survive into adulthood. Other studies in the literature have reported that adult with RTT have a milder phenotype and that cases with a more severe phenotype do not survive into adulthood (Colvin et al. 2004; Bebbington et al. 2010; Vignoli et al. 2012).

Mood disorders are being reported more commonly in individuals with ID. Previous studies reported that at least 1 in 10 people with ID suffer from mood disorders (Lowry 1998). Result from the longitudinal study suggested that level of mood decreases with ages and abnormal low level of mood is more common in adolescence (12 – 17 years old), confirming results from the cross-sectional study. Halbach et al. (2012) reported an increase in mood changes over a period of 5 years and an increase in behavioural problems, such increased level of anxiety and agitation in adults with RTT. Vignoli and colleagues (2012) reported behavioural problems in nearly half of their sample aged  $\geq 14$  years with 43% reported to have depressed mood and 46% agitation. There are no other studies to my knowledge that reports mood disorder in females with RTT over time so these findings are novel. Moreover, previous studies reporting low or depressed mood did not include standardised and validated instruments.

The second part of the study reported longitudinal data on family stress, anxiety and depression over 16 months. The study included only participants that were living at home.

In the first part of the analysis correlation between severity of behavioural presentation (as measured with the RSBQ) and parental negative experiences were explored. Results confirmed data from the cross-sectional study, indicating that severity of child behavioural presentation is associated with family stress, anxiety and depression.

In addition, examination of longitudinal changes in maternal negative experiences was explored. Analysis revealed that stress, anxiety and depression significantly increased over time. In particular, an increased number of mothers were rated in the borderline range of the Anxiety subscale and in the abnormal range of the Depression subscale of the HADS. A second set of analysis, using Linear Regression analyses were conducted to explore whether severity of behavioural problem would predict increased maternal stress, anxiety and depression. There was evidence of a relationship between increased severity of RTT behavioural presentation and maternal stress, anxiety and depression over time. Baker et al. (2003) and Hastings et al. (2006) reported similar findings. Both studies found evidence of a bidirectional relationship between child behavioural problems and maternal distress. In the present study the relationship between parental stress and child behavioural severity was not explored, however one could hypothesise that environmental condition (such as parents' distress, marital relationship, level of stimulation) would have an effect on the child behavioural presentation. The RSBQ does not measure level of aggressive or self-injurious behaviour, but is a measure of assessing severity of RTT clinical and behavioural presentation. In this study domain such General mood, Breathing abnormalities,

Fear/Anxiety and Repetitive face movement were associated with maternal stress, anxiety and depression. These findings were consistent with the cross-sectional data and as suggested by Laurvick et al (2006) in one of the few study exploring maternal well-being in family with children with RTT, the face movement domain which includes items such as makes mouth grimacing, grimacing expression may be linked to a more neurological severity thus the mother becomes more anxious. In this study a moderate association with breathing abnormalities was also found with maternal anxiety.

Laurvick et al. (2006) found an association between better maternal physical health and absence of breathing abnormalities such as hyperventilation, breath hold and deep breathing. The authors suggested a link between clinical severity and the presence of autonomic dysfunction. Thus they hypothesised that maternal well-being would be better in those with a child with a less severe phenotype. In addition, severity of behavioural presentations such as general mood and fear/anxiety were found to be associated with maternal stress, anxiety and depression. Problems with mood, fear and anxiety were found to be persistent over time, with no significant change over 16 months, indicating that is the presence of the behaviour that has an effect on maternal well-being. Whether these are just a RTT manifestation is to be explored further as this study did not include a control group for the RSBQ, however Mount et al. (2001) found that these behaviours were more prevalent in the RTT group when compared to a group of individuals with severe ID. Further studies should explore maternal well-being and behavioural problems using a well matched control group.

No other studies exploring longitudinal relationship between RTT behavioural presentations and maternal distress were found, thus it was not possible to compare results of this study with others.

There are some limitations this study to consider. Firstly the sample size was relatively small and although the age of the participants ranged from childhood to adulthood, the small size in each group limited the power of statistical analyses. Moreover, the study did not include a comparison group for the longitudinal study, thus a further study in the family well-being should include a well matched control group of family with children and adult with other rare genetic syndrome.

## CHAPTER 11

### A DESCRIPTIVE STUDY OF THE BEHAVIOURS OF GIRLS/WOMEN WITH RTT

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#### 11.1 Introduction

Very few studies have utilized systematic observation of the behaviour of people with RTT. The majority of those that have are single case studies that have explored a single behaviour, using experimental functional analysis. Such studies have reported inconsistent results. Overall, the question of the extent to which environmental variables may account for behaviour in girls/women with RTT remains largely unexplored.

Oliver et al. (1993) conducted an assessment of self-injury (SIB) in a child with RTT. Results indicated that the function of the behaviour was to terminate social contact, in particular physical contact or vocalisations, indicating that ongoing attention was an unpleasant situation from which the child wished to escape. However, the findings of Iwata et al. (1986) differed from those of Oliver et al. (1993) as the SIB (hand biting) of two females was shown to be independent of environmental circumstances. The SIB appeared to serve a self-stimulatory function in both girls, although it decreased in one case when food was presented contingent to toy play and with the application of Differential Reinforcement of Other behaviour (DRO) plus 10s restraint.

Despite their different results, both studies highlighted the importance of considering the environment in shaping the behaviour of girls/women with RTT and the possibility that, as indicated by Iwata et al. (1986), operant conditioning strategies may be successful in not only decreasing SIB but also increasing compliance and toy play. In

line with this, Roane et al. (2001) conducted a functional assessment of hand wringing and hand mouthing in two females with RTT in order to determine the influence of environmental variables in the maintenance of such stereotypies and explore whether there was a basis for intervention to decrease the behaviours. Results for both participants indicated that the hand wringing and hand mouthing occurred across all conditions at a high rate, consistent with internal, automatic as opposed to external environmental reinforcement. Weymeyer et al. (1993) and Wales et al. (2003) analysed the role of environmental stimuli in the frequency of hand stereotypies across four conditions (alone, demand, attention and leisure), following the model of functional analysis developed by Iwata et al. (1982). Weymeyer et al. (1993) found that repetitive hand movements were more frequent during the demand condition for one subject and the alone condition for another subject, indicating that maintaining reinforcement may vary between individuals and be either external or automatic. However, the findings of Wales et al. (2003) differed. Modification of environmental stimuli in their study did not influence the frequency of the stereotypies investigated. Their participants engaged in hand stereotypies for the majority of the time. Repetitive hand movements in some participants were observed for over 95% of the time, while the frequency for some others varied more but not consistently across environmental conditions. Their conclusion was in line with other studies utilizing analogue condition (Iwata et al. 1986; Roane et al. 2001), which suggested that stereotyped behaviour and self-injury are maintained by automatic reinforcement or neuro-chemical factors.

Although the weight of findings suggest that the high prevalence of repetitive hand movements stems from an organic cause, authors have nonetheless hypothesized that it might still be possible that environmental factors may be involved in their occurrence (e.g., Roane et al. 2001). For example, deprivation of stimulation must be considered.

Moreover, although analytic studies suggests that hand stereotypies serve a self-stimulatory function, there are few empirical studies that have investigated potential maintaining variables by manipulating actual as opposed to analogue environmental conditions.

Although the literature using operant conditioning with people with RTT is limited, other studies that include participants with other syndromes have demonstrated the influence of environmental events in maintaining and shaping behaviour. Taylor and Oliver (2008) analysed the association of self-injury and aggressive behaviour in five children with Smith-Magenis syndrome. They found an association between self-injury and decreased adult attention. Similarly, Arron et al. (2006) and Moss et al. (2005) using experimental functional analysis, reported an association between self-injury and environmental events in Cornelia de Lange syndrome.

The aim of this study was to observe and describe the behavioural repertoire of 11 females with RTT with confirmed *MECP2* mutation and how it was organized in relation to environmental events. To my knowledge, this is the largest study of this kind including both children and adults with a wide range of severities. Behavioural observation can be sensitive to subtle differences between individuals or within individuals over time. As RTT is a rare genetic syndrome, relevant behavioural and emotional manifestations may not be described in standardized scales. Thus direct observation can be an essential tool to describe qualitative differences in behaviour that cannot be measured by other means of assessment. Hence, the aim was to add to the literature on the behavioural characteristics of RTT and to the understanding about how behaviour may vary according to environmental conditions. Such investigation has the potential to identify optimal environmental conditions to deliver care and whether an

enriched environment would decrease the level of hand stereotypies and other behaviours typically seen within RTT.

## **11.2 Participants' characteristics**

Participants for the direct observational study were selected from survey participants who had a confirmed *MECP2* mutation. Twenty-five invitation letters were sent to families and 16 agreed to take part. However, due to the practicalities of travel, only 11 participants were visited.

Mean age of the 11 participants was 16.3 years (SD 9.38, range 5 – 32 years). Mean developmental age (measured with the VABS) was 12.6 months (SD 4.11, range 8 – 23 months). Mean developmental age score in the communication, daily living skills and socialization domains were 14.0 months (SD 7.54, Range 6- 34), 14.1 months (SD 3.47, range 11 – 23) and 11.2 months (SD 6.72, range 4 – 29). Nine (81.8%) of the participants included in the observation study were diagnosed with Classical RTT. The other two had diagnoses of Atypical RTT (1) and *MECP2* related disorder (1). The ability to walk was impaired in 7 (63.6%) of the participants, lost in 2 (18.2%) and normal in 2 (18.2%) (see Table 11.1).

All girls/women had a mild/less severe clinical severity phenotype (mean 6.36, SD 1.85, range 4 – 9). Hand use was reduced in 5 (45.5%) and lost in 6 (54.5%). All were reported to have hand stereotypies. Regression age ranged between 8 – 38 months, (mean 18.9, SD 8.80) (the participant with *MECP2* related disorder did not have regression).

## 11.1 Participants' characteristics

Participant	Chronological Age (years)	Developmental age (VABS in months)	Diagnosis	MECP2 mutation	Mobility	Severity Score	RSB Q Total
P1	11 yrs	11 months	Classic RTT	del.exon 4-3	Lost	8	34
P2	8 yrs	Not Available	Classic RTT	R255X	Impaired	8	69
P3	10 yrs	11 months	Classic RTT	P152R	Impaired	5	47
P4	5 yrs	13 months	Atypical RTT	c.116delGA	Lost	9	48
P5	5 yrs	8 months	Classic RTT	R294X	Impaired	6	45
P6	14 yrs	10 months	Classic RTT	P101L	Impaired	9	47
P7	23 yrs	11 months	Classic RTT	R294X	Impaired	6	58
P8	21 yrs	11 months	Classic RTT	R306C	Impaired	4	15
P9	32 yrs	13 months	Classic RTT	R306H	Impaired	6	46
P10	22 yrs	23 months	MECP2 disorder	C-Terminal	Normal	5	57
P11	28 yrs	15 months	Classic RTT	R306C	Normal	4	28

## 11.3 Procedures

The intention was to carry out direct behavioural observation in the natural environment (e.g., home, school or day centre). The observations were conducted over 7 months by video recording using a digital camcorder. The number and length of sessions varied between participants. Total times observed ranged from 1 hour and 28 minutes to 5 hours and 30 minutes, with an overall total across the 11 participants of 30 hours and 20 minutes. On some occasions, observation had to be stopped because the participant had a seizure, was not well or the presence of an extra person in the environment was too distressing.

Recordings were conducted in the participants' normal setting (home, school or day centre) during usual activities (leisure, meal time, group and individual activities). The

observer tried to be as discrete as possible during the sessions so as not to intrude on the activities of the participants. Parents and teachers were instructed to interact with the person as normal.

#### **11.4 Behavioural observational definitions and coding**

Behavioural categories were devised by reviewing the literature on the behavioural phenotype on RTT and formal discussion with supervisors. In addition to the behaviour of the person with RTT, parental/carer behaviour and environmental events were also defined and coded. Table 11.2 sets out behavioural categories and their definitions.

## 11.2 Behavioural categories and operational definitions

<b>Participant behaviour</b>	
<b><i>Engaged Activity</i></b>	
Involving the use of hands	Use of computer, switches, reaching for objects, manipulating toys or objects, taking objects to mouth, educational tasks, leisure, feeding, eating, self-help activity (for feeding, eating, self-help the person must be involved actively in the activity).
Not involving the use of hands	Listening to music, watching a DVD etc
<b><i>Social engagement</i></b>	
Eye contact	Looking at person for at least 3- 5 second or more to attract, maintain or end interaction.
Vocalization	Any sound or word to attract, maintain or end interaction
Movements	Defined and clear movements to attract, maintain or end interaction
<b><i>Disengaged</i></b>	
Disengaged	Passive or seemingly trivial movements, neither part of a constructive activity nor repetitive enough to constitute stereotypy nor sufficiently intense to constitute self-injury or aggression. Behaviour not directed towards any person or task.
<b><i>RTT behaviours/mood/episodes</i></b>	
Hand stereotypies	Repetitive movements of the hands that include wringing, tapping, rubbing washing movements, hand mouthing. The movements may be performed with hands together or hands apart.
Other stereotypies	Includes any other repetitive movements such as body rocking, bruxism, repetitive movements with the head, repetitive tongue movements, facial grimacing and repetitive vocalisations.
Self-injurious behaviours	Any behaviour that leads to physical harm or potential harm, including hitting own body, tapping/rubbing own body sufficiently to discolor skin, biting own body, scratching own body, hand biting, hair pulling, skin picking, banging own body (e.g., head) on fixtures (e.g., wall, table).
Aggression	Any physical act towards another person that leads to physical harm or potential harm, includes behaviours such as hair pulling, hitting, breaking property or objects. Any vocal aggression, including screaming, shouting, swearing at another person.
Mobility	Any behaviour when the child is moving around.
Mood	Clear emotional states: <ul style="list-style-type: none"> <li>• Positive vocalization/facial expression: i.e. smiling, laughing</li> <li>• Negative vocalization/facial expression: i.e. crying, screaming, sad expression.</li> </ul>
Breathing abnormalities	Hyperventilation, breath hold, valsalva
Rett Episodes	Identified as possible seizure, eye glaze is not fixed, appear not to be breathing, no hand movements, absence of motor activities (non epileptic behaviour).
<b>Parental/carer engagement</b>	
Giving assistance (Support)	Parent or carer helps the person to do an activity by, verbal or physical prompting, giving an

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		instructing, demonstrating or miming the activity or handing the person objects involved in the activity/placing objects in front of the person or engaged in parallel play/activity (i.e. doing an activity alongside the person as an activity partner). May involve helping the person to feed or drink but, in general, does not involve doing an activity for the person (e.g., brushing hair, washing hands)
	Help	Doing an activity to/for the person that involves attention/contact such as feeding, dressing, washing, grooming the person in a way that does not encourage the person's involvement (i.e. his or her role is passive).
		<b>Parents/carers interaction</b>
	Positive interactions	Parent or carer is interacting with the person in a positive manner but not in a way that gives assistance. i.e. praise, kissing/stroking the person, reading or singing to the person. The parent/carer must be involved with the person, giving attention.
	Neutral Interaction	Talking to the person in a way that neither encourages nor discourages activity (e.g., greeting the person, incidental remarks, commenting). Or physically contacting the person in a way that neither encourages nor discourages activity (e.g., holding hands, having the person sitting on lap).
	Restraint	<ul style="list-style-type: none"> <li>• Prevention: Physical actions or vocalisations to discourage activity (e.g., physical prevention of movements, hold hand to stop stereotypies, telling the person not to do something).</li> <li>• Mechanical restraint: for example the person is wearing an arm splint</li> </ul>
		<b>Setting Event</b>
	Alone	Nobody in the room
	Person in the room, not close	Any person, family member or carer in the room but not close. Defined as being not within 2 m.
	Person in the room, close	Defined as being within 1-2 m.

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The Engaged Activity category included self-help, domestic/work, leisure/ play or educational activity, e.g. simple early years actions that may be appropriate for the person's developmental level, such as mouthing an object or manipulating a rattle/sensory toy. Engaged Activity involving use of the hands was distinguished from that which did not involve the hands (e.g., looking at television or listening to a story). Social Engagement included all behaviours orientated towards another person to obtain and/or maintain interaction, e.g., vocalizing towards another person, maintaining eye

contact with a person talking to the person, reaching out towards a person or orienting to a person in response to physical or vocal contact. Parental/carer interaction (Positive Interaction, Neutral Interaction) and Engagement (Help and Support) variables were combined and a single variable, Adult Attention, created. A further category, Social Engagement was created by combining Eye contact, Movements and Vocalisation. In addition the categories Engaged in activities involving the use of the hands, Engaged in activities not involving the use of the hands and Social Engagement were combined into a single variable 'Engaged' and used only for the lag analysis.

All videos were coded using OBSWIN software (Martin et al. 2001). Observation categories are allocated a key on the computer keyboard, which for convenience are labeled with an abbreviated category name. OBSWIN uses real time analyses in which all categories occur in temporal sequence measured by elapsed time in seconds from the beginning of the session. Times of occurrence correspond to key depressions. The variables under observation can be recorded as events (a single key depression which indicates occurrence during a particular one-second window) or as durations (two key depressions which indicate onset and offset times).

For this study the onset and offset times of variables were recorded and percentages of intervals spent in each were then analysed. For the analysis, datafiles for each participant were appended separately for each setting (Home or school/day centre). This operation allows one to join continuous sessions in the order that they are selected (Martin et al. 2000).

### **11.5 Inter - rater reliability**

A second observer coded the first 15 minutes of each participant's observation session for inter-rater reliability, giving a total of 2hr and 45 minutes checked for reliability (8% of the total). Training was delivered to the second observer across several sessions by firstly viewing some videos and discussing the coding procedures and then coding the first 5 minutes of the videos until a good reliability was reached. The reliability of the video was checked and discussed with the second observer if there were discrepancies. For this study a 5s tolerance in the difference between observers was used when calculating agreement.

Cohen's kappa was calculated for each variable under observation. Cohen's kappa is a measure of agreement that takes into account agreement by chance. It has a range from 0-1. Kappa of <0.2 is considered poor agreement, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 strong, and more than 0.8 near complete agreement (Fleiss 1984). However, arising from the correction for agreement by chance, Kappa is particularly stringent if a behaviour occurs very rarely or nearly all of the time as it becomes increasingly difficult for the agreement between the two observers to be better than chance agreement. The calculation of kappa assumes that the frequency of occurrence of the category in question is known, whereas this is not the case, as it is this that the observation is attempting to establish. Kappa is, therefore, a poor guide to the reliability of observation for categories that have frequencies of occurrence that approach the extremes. For this reason, percentage occurrence agreement and percentage non occurrence agreement was also calculated.

Table 11.3 summarises mean Kappa values and percentage occurrence agreement and percentage non occurrence agreement across all variables under observation. Codes were divided in three categories: (1) reliably coded, with a kappa above 0.6, (2) on the

margins of reliably coded with a kappa between 0.41 – 0.60 and (3) unreliably coded with kappa equal and below 0.40. Codes in the latter category were considered unusable. The behavioural codes excluded included: *Mechanical restraint*, *Prevention*, *Other stereotypies* and *Positive mood*. However, the wearing of arm splints (*Mechanical restraint*) is described in the first section of the results, as percentage occurrence and non-occurrence agreement figures for this code were considered acceptable for descriptive data. For codes with a kappa of 0.41 – 0.60, percentage occurrence and non occurrence agreement was explored to examine whether the codes could be considered with confidence. For all codes, except *Breathing abnormalities* (62.34%) and *Disengaged* (70.39%), percentage occurrence agreement was above 90%. Percentage occurrence agreement of *Breathing abnormalities* ranged across participants between 0 – 96.7%. The behaviour was observed in 6 of the 11 participants. For two participants (P2 and P7), percentage occurrence agreement was poor (47.4% and 0%). For the remainder, it was above 64%. Due to poor agreement, *Breathing abnormalities* was excluded from further analysis for P2 and P7.

Percentage occurrence agreement of *Disengaged* ranged across participants between 1.1 – 100%. The *Disengaged* category for participants P1, P9 and P10 had poor percentage occurrence agreement (all below 39.5%) and were excluded for further analysis. Agreement for the remaining participants was above 86.7%.

The *Aggression*, *Mobility* and *Rett episodes* categories were not observed during the reliability coding.

**Table 11.3 Cohen's Kappa value and percentage of occurrences agreement**

	Mean Kappa	Range	% Occurrence	% Non Occurrence
Engaged in activity (hands)	0.69	0.78 – 1.00	73.77	86.78
Engaged in activities (No hands)	0.93	0.79 – 1.00	91.30	99.40
Disengaged	0.56	0.00 – 1.00	70.39	62.92
Eye contact	0.53	0-.00 - 0.88	46.21	96.68
Vocalization	0.57	0.00 – 0.92	53.10	94.40
Movements	0.92	0.92 – 0.92	85.71	99.95
Hand stereotypies	0.71	0.04 – 0.95	80.82	71.83
Other stereotypies	0.37	0.00 – 0.79	39.99	92.20
Self-injurious behaviours	0.48	0.21 – 0.75	37.50	99.33
Positive Mood	0.00	0.00	0.00	99.05
Negative Mood	1.00	1.00 – 1.00	100	100
Breathing abnormalities	0.49	0.00 – 0.87	62.34	83.70
Giving assistance (Support)	0.79	0.45 – 1.00	77.66	89.29
Help	0.91	0.70 – 1.00	90.43	97.14
Positive interactions	0.52	0.00 – 1.00	51.82	94.22
Neutral Interaction	0.50	0.00 – 0.89	44.04	94.13
Prevention	0.35	0.00 – 0.85	27.98	97.80
Mechanical Restraint	0.00	0.00	98.89	90.91
Alone	0.85	0.73 – 0.96	80.10	97.38
Vicinity	0.71	0.00 – 0.97	67.43	96.61
Proximity	0.87	0.74 – 1.00	98.13	82.41

## 11.6 Data Analysis

In the first part of the analysis, the percentage of time (intervals) that each behaviour or environmental condition occurred was calculated for each setting (home or school/day centre).

In the second part, variability in participants' levels of engagement in activity or social interaction together with the level of adult attention each received was associated with the participants' skill levels (as measured with the severity score and the age equivalent score of the VABS).

In the third part, variability of participant behaviour across environmental conditions was analysed. This was done using lag analysis, set to Lag 0. Lag 0 denotes the co-

occurrence of the target and criterion variable at the same time. In this case, the target is the participant's behaviour and the criterion is the environmental condition.

The conditional probability of a behaviour occurring given a certain environmental event or other behaviour was calculated. The calculation of a conditional probability (P) involves dividing the number of intervals in which the behaviour occurs in the presence of a certain environmental state by the total number of intervals in which the environmental state is present. If the conditional probability differs from the unconditional probability of the target behaviour, then the environmental condition may be considered to influence the behaviour.

Conditional and unconditional probabilities can be used to calculate odds ratios. The odds ratio computes the ratio of the likelihood of a target event occurring or not given the presence or absence of the criterion event. Under the null hypothesis a formula based on the quantities in a typical 2 x 2 table, with cells a, b, c, d, is distributed as chi-square and this may be used to test for significance.

The odds ratio varies from 0 (perfect negative relationship), through 1 (no relationship) to infinity (perfect positive relationship). Yule's Q, a simple arithmetic transformation of the odds ratio  $[(ad-bc)/(ad+bc)]$ , preserves the rank ordering of the data and establishes a more conventional range to the index so that -1 depicts a perfect negative relationship, 0 no relationship and +1 a perfect positive relationship (Bakeman et al. 1996). Yoder and Feurer (2000) proposed that Yule's Q is the most appropriate index of association as it controls for the probability of the target and criterion events while quantifying the association between them. Yule's Q was, therefore, used to evaluate the magnitude of an association between variables. A Yule's Q of  $\pm 0$  to  $\pm 0.29$  was interpreted as a small association; Yule's Q  $\pm 0.30$  to  $\pm 0.49$  moderate;  $\pm 0.50$  to

$\pm 0.69$  as substantial association and Yule's Q  $\pm 0.70$  and above is very strong (Davis 1971 cited in Bernard 2000). OBSWIN was used to perform all analyses.

Based on the above, only Yule's Q with an absolute value  $\geq 0.30$  were considered for further discussion. Moreover, Yule's Q with an absolute value =1 were treated with caution. Ott et al. (1992) argued that if one of the values in the 2x2 contingency table is equal to 0, this will result in a Yule's Q of  $\pm 1$ . Thus, if the absolute value of Yule's Q is equal to  $\pm 1$  it does not necessary indicate a perfect association between the two variables.

The significance of Yule's Q was evaluated with the following equation (Sheskin 1997):

$$Z = \frac{Q}{\sqrt{(0.25)[1-(Q)^2]^2[1/a+1/b+1/c+1/d]}}$$

Using the z score together with an index of association (Yule's Q) would allow a better understanding of the data. However one of the limitations of the use of the z score is that its value is influenced by the number of occurrences of the target behaviour. The z score increases as the total number of observation intervals increases (Bakeman and Gottman 1997). Due to the number of tests performed, the alpha level was reduced. A significant level of association was evidenced by a z score above 3.09 ( $p > .001$ ).

Finally in the forth part, time sequential analysis was used to examined the relationship between participants' behaviour and Adult attention using time-based (5s) lag analysis. Time-based lag analysis was used to calculate the conditional probability

of the target behaviour being present given the onset of Adult attention. Conditional probability refers to the probability of a particular behaviour, i.e. breathing abnormalities, occurring given the occurrence of another event, e.g. adult attention (Bakeman and Gottman 1997).

Comparison of lagged conditional probabilities and unconditional probabilities is conceptually similar to the comparison of unlagged conditional probabilities and unconditional probabilities above. Yule's Q and associated z scores were calculated in the same way.

## **11.7 Results**

### **11.7.1 Percentage duration of environmental conditions and behavioural states**

The following section summarises the percentages of time that participant behaviours and environmental conditions occurred across settings (home and school/day centre). All participants were observed at home but only 6 (54.5%) could be also observed at school or day centre.

P2, P4, P5 and P6 wore arm splints at home and school/day centre: P2 for 18.1% of the time at home and 14.1% at school, P4 for 58.3% at home, P5 for 58.1% at home and 62.7% at school/day centre and P6 for 92.3% at home and 59% at school/day centre.

In general, participants were mainly in adult company and received attention at a high rate (see Table 11.4). The mean percentages of time when participants were Alone or in the Vicinity condition were respectively 17.5% (SD 19.47, range 0 – 63.5%) and 11.0% (SD 11.2, 0.04 – 29.5%) at home and 0.0% and 7.3% (SD 6.1, range 0 – 15.3) at school/day centre. Adults were in close Proximity for an average of 70.9% (SD 20.12, range 15.8 – 90.2) of the time at home and 92.1% (SD 6.19, range 84.4 – 99.9) at

school/day centre. On average, participants received adult attention for 57.7% of the time at home (SD 24.55, range 14.9 - 86.8%) and for 77.5% of the time at school (SD 13.84, range 56.1 – 92.4%).

**Table 11.4 Percentage duration of time in each environmental condition at home**

	Alone		Vicinity		Proximity		Adult Attention	
	Home	School/ Centre	Home	School/ Centre	Home	School/ Centre	Home	School/ Centre
P1	0.3	-	0.66		98.92	-	84.2	-
P2	0.8	0.0	0.04	9.1	97.50	90.8	82.0	89.4
P3	33.2	0.0	2.86	13.1	63.93	85.8	35.8	70.2
P4	13.1	-	13.05	-	73.69	-	35.5	-
P5	27.5	0.0	4.19	15.3	65.41	84.4	62.2	72.0
P6	18.5	0.0	17.26	3.4	64.19	96.2	55.4	92.4
P7	9.9	-	28.03	-	61.89	-	39.2	-
P8	63.5	0.0	20.55	3.0	15.83	95.1	14.9	56.1
P9	0.0	-	1.41	-	98.44	-	82.0	-
P10	25.8	-	29.53	-	44.49	-	59.3	-
P11	0.0	0.0	3.82	0.0	09.01	99.9	86.8	84.7

The percentages of time that participants were engaged in social, daily living, recreational or educational activities at home and at school/day centre are set out in Tables 11.5. Participants were engaged in activity involving the use of the hands for an average of 19.2% (SD 19.8, range 0 – 54.1%) of the time at home and 22.4% (SD 19.18, range 2.5 – 46.6%) of the time at school/day centre. They were engaged in activities that did not involve the use of the hands for an average of 29.6% (SD 27.1, range 0 – 85.7%) of the time at home and 20.8% (SD 16.13, range 4.2 – 42.2%) of the time at school/day centre. Time spent in social interaction averaged 16.8% (SD 17.37, range 1.44 – 57.1%) at home and 20% (SD 17.0, range 2.8 – 46.0%) at school/day centre. For 30% (SD 25.9, range 0 – 79.4%) of the time, participants were observed to be disengaged at home. The figure for school/day centre was 34.4% (SD 20.57, range 13.9 – 63.8%).

**Table 11.5 Percentage duration of time engaged in activity or disengaged for each participant**

	Disengaged		Engaged Activity (hands)		Engaged Activity (no hands)		Social engagement	
	Home	School/Centre	Home	School/Centre	Home	School/Centre	Home	School/Centre
P1	3.6	-	0	-	85.7	-	11.3	-
P2	35.0	56.4	0	4.8	46.7	4.2	10.0	15.1
P3	6.15	13.9	36.1	14.8	46.2	42.2	20.9	35.5
P4	74.4	-	0.8	-	1.2	-	1.9	-
P5	22.0	19.7	24.0	21.0	11.6	15.2	22.3	46.0
P6	58.7	63.8	1.7	2.5	8.5	7.3	1.4	2.8
P7	58.3	-	0	-	35.8	-	2.7	-
P8	22.6	24.6	54.1	46.6	13.9	16.8	6.1	13.5
P9	19.5	-	28.0	-	18.7	-	38.7	-
P10	0.0	-	43.1	-	0.0	-	57.1	-
P11	14.5	28.1	23.6	44.5	57.8	39.2	12.5	7.1

The most common activities in which participants were engaged were: watching TV, listening to music, listening to a story book and early learning activities involving simple manipulative toys, switches and water. Five of the participants were observed to feed themselves. Some of the participants clearly showed interest in the activities that they were engaged in. For example P1 spent the majority of the time watching a preferred DVD or listening to a story and during this time she appeared interested in the activities and few hand stereotypies were observed. Other participants showed less interest even when engaged. Three participants were disengaged for most of the time.

Tables 11.6 summarises the percentages of time participants engaged in hand stereotypies, breathing abnormalities and self-injury in each setting (home and school/day centre). All participants, except one, were observed to have hand stereotypies. Six of the 11 participants had breathing abnormalities (albeit observation was unreliable for two) and 6 out of the 11 participants were observed to display self-injurious behaviour. Apart from the occurrence of hand stereotypies for P2 and P5,

occurrence of hand stereotypies, breathing abnormalities and self-injury was similar at home and at school/day centre. The different rates of hand stereotypies for P2 and P5 appeared unrelated to the wearing of arm splints, as this occurred similarly in each setting for both participants. Moreover, P6 wore arm splints much more at home and yet occurrence of hand stereotypies did not vary between settings. It is possible that the higher rate of hand stereotypies at school for P2 was related to her seeming upset, which may have been associated with gastro-intestinal pain, which she was known to experience.

**Table 11.6 Percentage occurrence of stereotypies, breathing abnormalities and self-injury**

Participants	Hand stereotypies		Breathing Abnormalities		Self-Injury	
	Home	School/Centre	Home	School/Centre	Home	School/Centre
P1	19.3	-	0.0	-	8.9	-
P2	32.5	59.7	unreliable		0.0	0.0
P3	99.4	89.8	30.2	22.5	0.0	0.0
P4	62.2	-	78.9	-	6.2	-
P5	71.2	22.9	18.4	14.9	1.9	1.7
P6	61.2	54.1	49.9	44.5	6.0	1.5
P7	94.6	-	unreliable		2.8	-
P8	33.9	40.9	0.0	0.0	0.0	0.0
P9	54.5	-	0	-	0	-
P10	0.1	-	0.0	-	0.0	-
P11	0.0	0.0	0.0	0.0	0.0	0.9

The topographies of hand stereotypies, breathing abnormalities and self-injury observed are set out in Table 11.7. Hand stereotypies observed included: hand wringing – hands apart, hand flapping – hands apart, hand wringing, hand mouthing, hand clapping and holding hands together. Breathing abnormalities observed included: hyperventilation, forceful expulsion of the air, breath holding and valsalva manouvre.

Self-injurious behaviour observed included: biting the hand, biting the arm, biting the fingers, hitting the head with the fist and hitting the mouth.

**Table 11.7 Topography of stereotypies, breathing abnormalities and self-injury**

<b>Participants</b>	<b>Hand stereotypies</b>	<b>Breathing Abnormalities</b>	<b>Self-Injury</b>
P1	Hand wringing – hand apart Hand mouthing	NA	Finger biting
P2	Hand wringing – hands apart	Hyperventilation Breath hold	NA
P3	Hand flapping – hands apart Hand wringing – hands apart	Forceful expulsion of the air	NA
P4	Hand tapping –hand apart	Breath hold Hyperventilation	Hitting the mouth
P5	Hand wringing -Hand together Hand tapping Hand mouthing	Breath hold Forceful expulsion of air	Finger biting
P6	Hand wringing Hand mouthing	Breath hold Hyperventilation Valsalva Manouvre	Finger biting
P7	Hand wringing	Breath hold Hyperventilation	Biting hands/arm Banging fist on head
P8	Hand mouthing Hand clapping	NA	NA
P9	Hand together	NA	NA
P10	Hands together	NA	NA
P11	NA	NA	Hitting the mouth

### **11.7.2 Association between levels of engagement in activity, social engagement and adult attention each received and participants’ skill levels**

Correlation analysis<sup>11</sup> revealed a significant negative association between participants’ level of engagement in activity involving the use of the hands and the severity score both at home and school/day centre (Home:  $r = -.687, p < .05$ ; School/Day centre:  $r = -.828, p < .01$ )<sup>12</sup>. Levels of engagement in activity not involving

<sup>11</sup> Kolmogorov-Smirnov test of normality revealed that data for the observations were normally distributed except for participants’ engagement (Hands) and Parental/carer Neutral Interaction. Thus both parametric and non-parametric correlations will be reported here

<sup>12</sup> Spearman was used for this analysis but parametric analysis using the Pearson statistic revealed similar results (Home:  $r = -.823, p = .002$ ; School/Day centre:  $r = -.894, p < .05$ ).

the use of the hands, social engagement and adult attention received were not significantly associated with the severity score.

Level of engagement in activity involving the use of the hands was also significantly associated with the abilities to hold and reach for an object (Home:  $r = -.874$ ,  $p < .001$ ; School/Day centre:  $r = -.828$ ,  $p < .05$  for both hold and reach objects). These skills were not associated with the level of engagement in activity not involving the use of the hands nor overall receipt of adult attention. However, the skills of holding and reaching for objects were associated with the level of assistance given at home ( $r = -.693$ ,  $p < .05$ ) and the level help given at school/day centre ( $r = .891$ ,  $p < .05$ )<sup>13</sup>.

In addition, there was a significant association between participants' Vineland age equivalent scores age and their level of social engagement at home ( $r = .696$ ,  $p < .05$ )<sup>14</sup>, but not their engagement in activities (with or without hands). Moreover, their age equivalent scores for the communication domain were significantly associated with their engagement in activity involving the use of the hands ( $r = -.739$ ,  $p < .05$ )<sup>15</sup>. Level of parental assistance was also related to the age equivalent scores for the communication domain ( $r = .720$ ,  $p < .05$ ). No significant associations were found for the school/day centre data.

### **11.7.3 Co-occurrence of behaviour and environmental conditions**

Analysis of the association between adult attention and the level of participants' engagement in activities, social engagement and disengagement revealed some strong associations, although these were not always consistent across participants or settings (see Table 11.7). Six of the 17 possible associations between adult attention and

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<sup>13</sup> Non-Parametric test revealed similar significant results,  $r = .828$ ,  $p < .05$

<sup>14</sup> Parametric test were reported for this analysis as the K-S showed that the data was normally distributed for VABS developmental age and Social engagement

<sup>15</sup> Non Parametric test were used for both analyses as K-S showed a non normal distribution of the data

engagement using hands were significantly positive, 4 significantly negative and 7 non-significant. Eight of the 16 possible associations between adult attention and engagement not using hands were significantly positive, 3 significantly negative and 5 non-significant. Fifteen of the 17 possible associations between adult attention and social engagement were significantly positive and 2 non-significant. Two of the 16 possible associations between adult attention and disengagement were significantly positive, 11 significantly negative and 3 non-significant.

**Table 11.8 Co-Occurrence between Adult attention and participants' level of engagement in activity showing significant Yule's Q**

	Disengaged		Engaged in activity (Hands)		Engaged in activity (No Hands)		Social Interaction	
	Home	School/ Centre	Home	School/ Centre	Home	School/ Centre	Home	School/ Centre
P1	- 0.55	-	†	-	- 0.51	-	+ 0.83	-
P2	†	- 0.46	†	†	†	+ 1.00	+ 0.30	+ 0.56
P3	- 0.65	- 0.77	+ 0.51	+ 0.87	- 0.75	+ 0.80	+ 0.80	†
P4	- 0.94	-	†	-	*	-	+ 0.91	-
P5	- 0.98	-0.80	+ 0.44	-	†	†	+ 0.87	+ 0.42
P6	- 0.84	- 0.54	+ 1.00	+ 1.00	+ 0.32	+ 1.00	+ 0.96	+1.00
P7	+ 0.96	-	-	-	+ 0.52	-	+ 0.63	-
P8	- 0.69	†	†	- 0.70	+ 0.33	+ 0.77	+ 0.86	+ 0.59
P9	†	-	- 0.79	-	+ 0.90	-	†	-
P10	^	-	- 0.85	-	NA	-	+ 0.97	-
P11	- 0.78	+ 0.37	†	†	†	- 0.36	+ 0.97	+ 0.42

\*Indicates that the two behaviours do not occur together. Yule's Q = -1.00

^ Not included in the analysis due to poor reliability agreement

† Not significant association

The association between hand stereotypies and the level of participants' engagement in activities was often significant but again was not consistent across participants and settings (see Table 11.8). Four of the 15 possible associations between hand stereotypies and engagement using hands were significantly positive, although 3 of the 4 were equal

to 1.00 and should be regarded as potentially unsound<sup>16</sup>. Eight were significantly negative and 3 non-significant. Four of the 15 possible associations between hand stereotypies and engagement not using the hands were significantly positive, although 1 of the 4 was equal to 1.00 and should be regarded as potentially unsound. Five were significantly negative and 6 non-significant. Eight of the 13 possible associations between hand stereotypies and disengagement were significantly positive, although 1 was equal to 1 and should be regarded as possible unsounded. One was significantly negative and 4 non-significant. Four of the 15 possible associations between hand stereotypies and adult attention were significantly positive, although 1 of the 4 was equal to 1.00 and should be regarded as potentially unsound. Five were significantly negative and 6 non-significant.

There seemed little consistent relationship between breathing abnormalities and engagement in activity using the hands as there were similar numbers of positive, negative and non-significant associations. Those between breathing abnormalities and engagement not using the hands tended to be significantly positive while those between breathing abnormalities and adult attention tended to be significantly negative. The association between breathing abnormalities and disengagement was mainly significantly positive.

Associations between self-injury and participant behaviour/adult attention can be summarized thus: those with engagement using hands were either positive or non-significant, with engagement not using hands were, with one exception, positive or non-significant, with adult attention, with one exception, negative or non-significant and with disengagement positive or non-significant.

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<sup>16</sup> A perfect positive association (Yule's  $Q = +1.00$ ) between the target behaviour and another event may indicate that the behaviour does not occur in the absence of the other event or that the behaviour occurs all the time regardless of the condition. For example, this was the case for hand stereotypies for P3.

**Table 11.9 Yule's Q  $\geq \pm 0.30$  in the home and school/day centre setting**

Partici pant	Behaviours	Disengaged		Engaged Activity (hands)		Engaged Activity (no hands)		Adult Attention	
		Home	School/ Centre	Home	School/ Centre	Home	School/ Centre	Home	School/ Centre
P1	Hand stereotypies	^	-	-	-	- 0.52	-	+ 0.93	-
	SIB	^	-	-	-	†	-	+ 0.88	-
P2	Hand stereotypies	†	+ 0.44	†	- 0.86	†	†	- 0.31	†
P3	Hand stereotypies	+ 1.00	+ 0.89	+ 1.00	+ 1.00	- 0.56	- 0.56	+ 1.00	- 0.48
	Breathing Abnormalities	+ 0.74	†	- 0.97	- 0.94	+ 0.51	†	- 0.41	- 0.36
P4	Hand stereotypies	†	-	- 0.83	-	+ 1.00	-	†	-
	Breathing abnormalities	+ 0.89	-	+ 1.00	-	+ 0.66	-	- 0.83	-
	SIB	+ 0.80	-	+ 1.00	-	+ 0.51	-	- 0.69	-
P5	Hand stereotypies	+ 0.93	+ 0.38	- 0.80	- 0.81	- 0.43	†	- 0.70	- 0.33
	Breathing Abnormalities	†	†	†	†	+ 0.38	†	- 0.40	†
	Self-injury	†	+ 0.42	+ 0.44	†	+ 0.57	†	†	- 0.61
P6	Hand stereotypies	+ 0.57	- 0.41	+ 0.57	- 0.63	†	- 0.33	- 0.50	†
	Breathing Abnormalities	+ 0.50	†	- 0.65	+ 0.87	†	- 0.85	- 0.48	†
	Self-injury	NA	+1.00	NA	*	NA	*	NA	- 0.92
P7	Hand stereotypies	†	-	†	-	+ 0.57	-	†	-
	Self-Injury	+ 0.60	-	†	-	- 0.55	-	- 0.44	-
P8	Hand stereotypies	+ 0.64	+ 0.50	- 0.79	- 0.69	+ 0.51	+ 0.54	†	+ 0.69
P9	Hand stereotypies	^	-	- 0.96	-	†	-	+ 0.51	-
P10	Hand stereotypies	^	-	+ 1.00	-	†	-	†	-
P11	Self-Injury	NA	*	NA	*	NA	+1.00	NA	- 0.40

\*Indicates that the two behaviours do not occur together. Yule's Q = -1.00

† Not significant association

^ Not included in the analysis due to poor reliability agreement

## 11.8 Sequential analysis

The fourth part of the analysis comprised a sequential analysis of the relationship between participants' behaviour and the receipt of adult attention. Time based sequential analysis was conducted to calculate the conditional probability of the presence of the participants' behaviour as the target (i.e., engagement, disengagement, hand stereotypies, breathing abnormalities, self-injury) occurring given the onset of the criterion variable, adult attention. The analysis explored the probability of the target behaviour occurring within 5s intervals up to 100 seconds prior and up to 100 seconds following the onset of adult attention.

Figures 11.1 and 11.2 show the results of the sequential analysis of disengagement and engagement given Adult attention at home and at school/day centre. There were no clear relationships for P1 or P2. For P3, P5 and P8, disengagement decreased and engagement increased following adult attention at home, but not at school. The unconditional probability of being disengaged for P4 was very high and that of being engaged was very low. Adult attention had no impact on the level of disengagement and little on the level of engagement. The conditional probability of engagement given attention was significantly reduced prior to receipt of attention and significantly increased afterwards, albeit in a fluctuating way. Adult attention appeared to have no effect, or at least no consistent effect, on disengagement and engagement for P6, P7, P9 and P11. The unconditional probability of being engaged was very high for P10. There was a slight indication that the level of engagement was below that level before receipt of attention and above it afterwards. In summary, there was evidence that adult attention increased engagement in constructive activity in just under half of the participants.

In general, analysis of the relationship between hand stereotypies and adult attention showed either no or no consistent pattern (see Figure 11.3).

The relationship between breathing abnormalities and adult attention is given in Figure 11.4 for the four participants for whom they were observed. In all cases, attention appeared to have no effect on the occurrence of breathing abnormalities. However, for three of the four participants at home, the data suggest that the occurrence of breathing abnormalities might affect the likelihood of adult attention. In two (P4 and P6 at home), the conditional probability of breathing abnormalities given attention was above the unconditional probability of breathing abnormalities both before and after the onset of attention, indicating that breathing abnormalities might attract adult attention. In the case of P3 at home, the opposite was the true.

Self-Injurious behaviours were observed in six participants. Results of the lag analyses are shown in Figure 11.5. There was no consistent pattern across participants and, for some, adult attention appeared to make no difference to the occurrence of self-injury, the conditional probability being either below (as in P1 at home) or above (as in P11 in the day centre) the unconditional probability both before and after the onset of attention. However, in three cases (P4 at home, P6 at school and P7 at home), there was evidence of the conditional probability being above the unconditional probability before the onset of attention and below it subsequently, suggesting a possible attention seeking motivation. Moreover in a fourth case (P5 at home), there was evidence of the conditional probability being below the unconditional probability before the onset of attention and above it subsequently, suggesting a possible avoidance motivation.

## **11.9 Discussion**

Systematic observation was conducted to explore the frequency of various behaviours manifested by 11 girls/women with RTT and a confirmed *MECP2* mutation. The behavioural observations were conducted in the day-to-day natural environment of

the participants with a view to analysing the relationship between certain environmental conditions and participants' behaviour. This study is novel as the sample included participants ranging from childhood to adulthood. Construct validity of the data is affected by the location in which the observations take place. Here, the findings are representative of typical life as all observations were conducted in the participants' typical every day settings, although it is not known what effect filming may have had on the events observed. Behavioural codes were operationally defined and reliability checks showed that, in most cases, behaviours were reliably identified and recorded.

A number of interesting findings emerged from the analysis. Firstly, participants were in the company of an adult (either parent or teacher or carer) for the majority of time, who interacted with the person with RTT for over half of the time by engaging in an activity for the person (feeding), supporting the participants to do an activity (by doing an activity alongside the person or prompting them) or by interacting with the person (reading a story to the person). Compared to data from residential settings for individuals with severe ID, individuals with RTT received a high level of adult attention in the form of positive interaction, assistance or help. For example, in an observational study of 40 individuals with severe ID, Emerson et al. (1999) reported that participants spent nearly 80% of their time with no contact from staff, 12% receiving assistance, 3.4% receiving care and 4.2% some other form of contact such as positive interaction. In contrast, data from this study indicated that the girls/women with RTT received positive interaction for about 27% of the time at home and 17% of the time at school/day centre. Individuals with RTT are reported to be very sociable and after the regression stage the girls/women become more responsive to their environment. It is possible that the presence of the observer may have influenced the level of engagement and interaction of the parents and carers observed. Although parents, school teachers

and day centre staff were instructed to interact with the participant as usual, they may have felt that they had to interact or engage with the girls/women more due to the presence of the observer. However, this might also have been true of staff in the observational studies of residential settings

The levels of participants' engagement in activities and social interaction were also relatively high compared to data from studies of residential services and their level of disengagement was lower. The girls/women in this study were recorded to be disengaged for about 30% of the time both at home and school. In contrast, Emerson et al. (1999) reported that participants were in the passive state for 54% of the time engaged in activities for 16% of the time.

The study identified a number of factors which were associated adult attention and participant's skills. Those with a more severe clinical phenotype were less likely to be engaged in activities involving the use of the hands and the girls that were able to reach and hold objects were more engaged in activities involving the use of the hand. In particular participants that had still this ability retained were more able to finger feed, feed with a spoon. It was also clear that parents gave more assistance in the form of instruction and physical prompts to those girls that could hold and reach objects. In addition, the communication domain age equivalent score of the VABS was associated with level of parental assistance and engagement in activities involving the use of the hands. These results are in line with studies in residential settings, which have indicated that individuals with more severe ID are less likely to engage in purposeful activities and may even receive less assistance to do activities, despite their greater need for it (Felce et al. 1996, Felce and Perry 2004).

The challenging behaviours most often observed were hand stereotypies, breathing abnormalities and self-injurious behaviour. All girls/women, except one (P11) were

observed to engage in hand stereotypies, such as hand wringing, clapping or mouthing. Two of the older participants (P9 and P10) did not perform any movements with their hands but they both held them clasped together. Hands stereotypies were recorded for more than 50% of the time for 6 of the participants and were constant for two. Hand stereotypies tended to be more frequent in the home environment but their occurrence was not significantly different across settings except for P2 and P5. The reason for this difference was not clear. Both participants were observed to wear arm splints equally at home and school. The higher frequency of hand stereotypies could be linked to the type of activities in the two settings. In addition, P2 was observed to experience gastrointestinal pain at school which could be associated with increased frequency of hand stereotypies. However this aspect could not be explored in this study and further research of the association between level of distress caused by pain and increased level of hand stereotypies, breathing abnormalities and self-injurious behaviour is recommended.

Breathing abnormalities, such as hyperventilation, breath holding and forceful expulsion of the air was only observed in the younger girls. None of the older participants had visible respiratory problems. In two of the participants (P2 and P7) the data regarding breathing problems were not included in the analysis due to poor inter-reliability agreement. Other studies exploring the behavioural repertoire of RTT have indicated that breathing abnormalities tend to be less severe in older individuals (Halbach et al. 2012, Cass et al. 2003, Halbach et al. 2008, Ellaway et al. 2001, Kerr et al. 1999, Julu et al. 2001). Self-injurious behaviour, observed in 6 of the 11 girls were recorded for an average of 5.2% of the time at home and 1.4% of the time at school/day centre. Self-injurious behaviours are often reported in RTT but are not part of the current diagnostic criteria. Early studies reported a high percentage of self-injurious

behaviour in RTT. Samson et al. (1993) and Coleman et al. (1988) reported rates of self-injury of 48.6% and 49%. SIB is commonly reported in children and adults with other genetic syndromes and may also be related to environmental stimuli (Moss et al. 2005, Arron et al. 2006, Taylor et al. 2008).

Results from the co-occurrence analysis in general indicated that adult attention was related to increased engagement and decreased disengagement, although there was not consistency across all participants. There was also some evidence of such relationships in the sequential analyses. Hand stereotypies generally occurred less when participants were engaged using their hands and more when they were disengaged, although again there was inconsistency across participants. There was little evidence of an association with adult attention in either the co-occurrence analysis or sequential analysis.

Breathing abnormalities tended not to occur during adult attention. However, the sequential analysis suggested that adult attention had no effect on the occurrence of breathing abnormalities but that the latter might attract adult attention. Self-injurious behaviour occurred less while participants received adult attention. This is consistent with the suggestion of an attention-seeking motivation in the sequential analyses for three participants but not with a possible avoidance motivation suggested for a fourth.

For two of the participants (P4 and P6), occurrence of breathing abnormalities was very high. In particular for P4, the abnormalities were nearly constant, which included hyperventilation and breath holding. Breath holding occurred on a regular basis for P4 and the girl appeared happy after an episode of breath holding. Hyperventilation was often accompanied with increased hand stereotypies and other stereotypies, such as teeth grinding, tongue protrusion and agitation. Breathing abnormalities such as valsalva type were often observed in P6. This type of breathing abnormality causes a decrease in blood pressure and an increase in heart rate due to pressure in the thorax

which prevents the blood returning to the heart. At the end of the valsalva manoeuvre the person is forced to expel the air out which causes a rush of blood back to the heart. This causes a decrease in heart rate and increased blood pressure which can cause panic and dizziness for the person with RTT. Moreover, severe breathing abnormalities also cause severe distress and anxiety for the parents. This may underlie the observation that such episodes attracted adult attention.

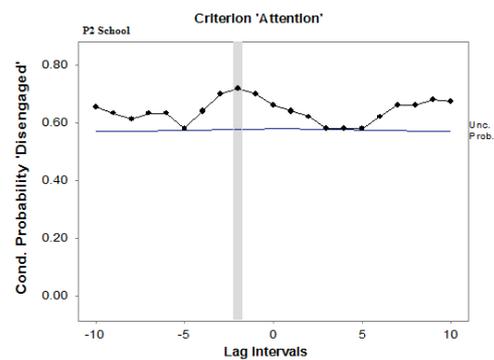
Stereotyped hand movements and breathing abnormalities are considered to be characteristic features of RTT and among the essential diagnostic criteria. The behaviours are thought to have an organic aetiology independent of environmental influence. Sequential analysis did not reveal any consistent relationships with environmental conditions. This fits with the existing literature. Wales et al. (2004) found that environmental manipulation had no effect on the hand stereotypies of 8 girls. Wehemeyer et al. (1993) found that the hand stereotypies of 2 girls with RTT did occur more or less frequently in various analogue conditions but that they were more likely to occur during the demand condition for one participant and during the alone condition for the other. Nonetheless, it is important to highlight that environmental conditions were not manipulated in this study. Correlational evidence based on the observation of naturally occurring conditions is not as powerful or definitive.

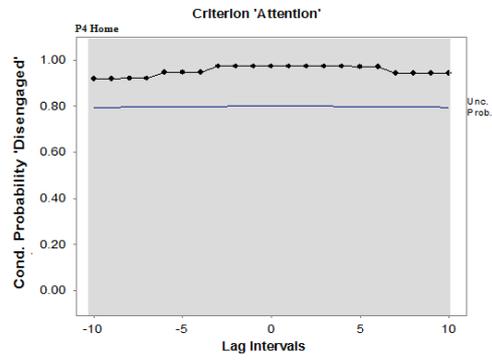
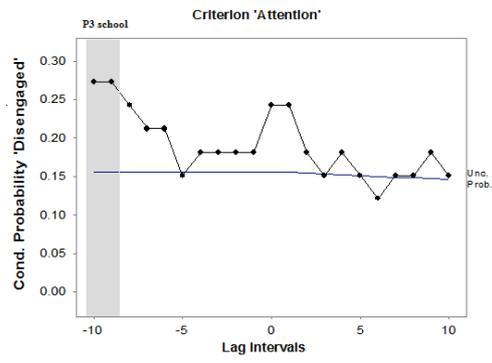
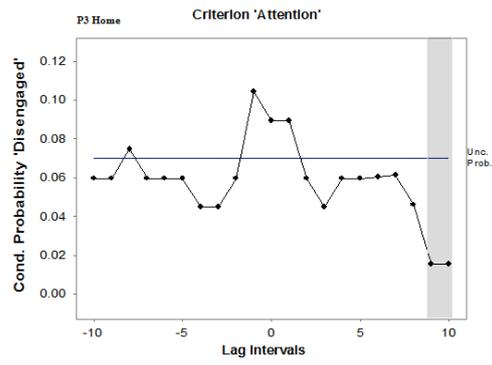
Self-injury is not an essential diagnostic criterion for RTT and as has been shown only occurs in a proportion of participants. Research has shown both that it may be maintained by environmental stimuli or be apparently internally driven. This study indicated that SIB might be related to social attention, either through positive reinforcement or escape/avoidance. Again, it is important to emphasize that this study did not constitute an experimental functional analysis. However, its findings do suggest

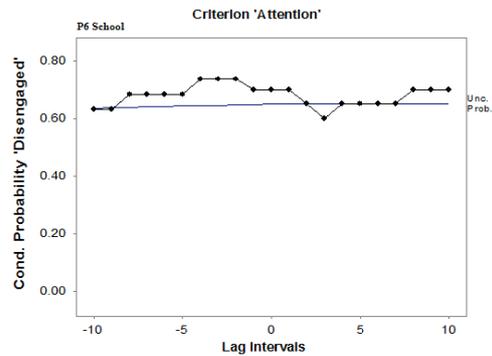
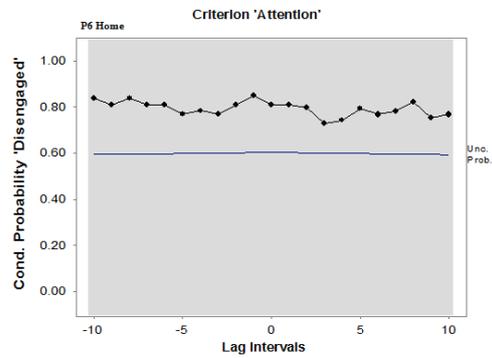
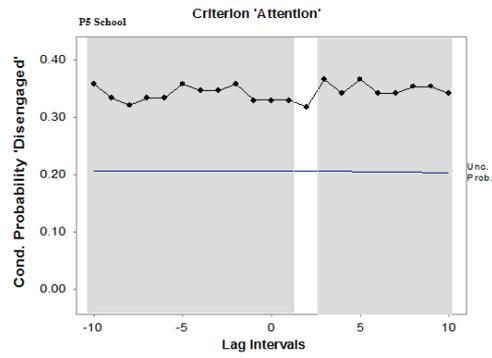
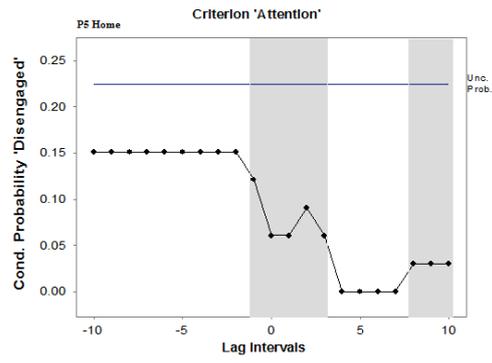
that conducting such an analysis would be important in clinical practice in order to examine the potential functions maintaining the behaviour.

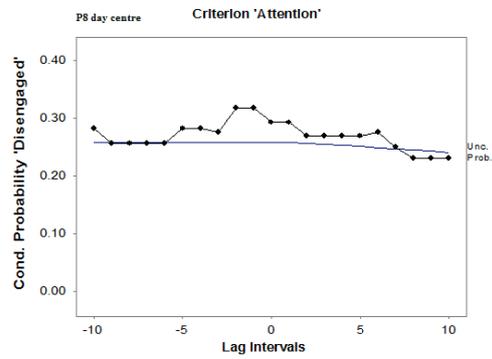
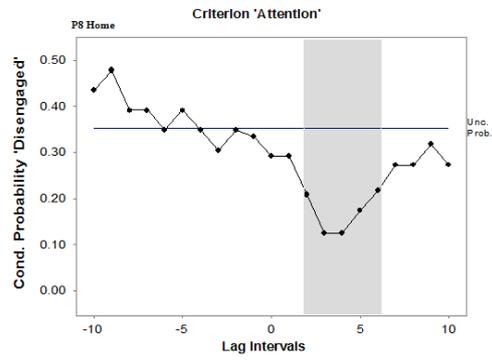
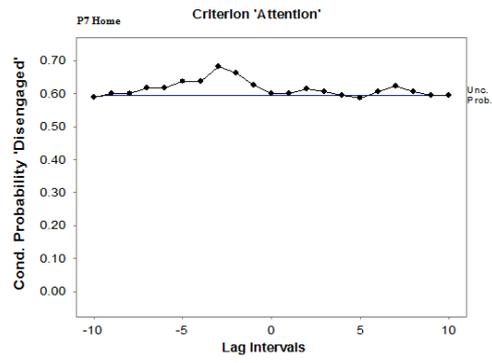
Despite the inconsistency of results across participants, the study highlighted the importance of considering the role of the environment in shaping the behaviour of girls/women with RTT. Enriching the environment may be a useful and successful strategy for decreasing unwanted behavioural manifestations and a structured learning environment may increase engagement in constructive activities.

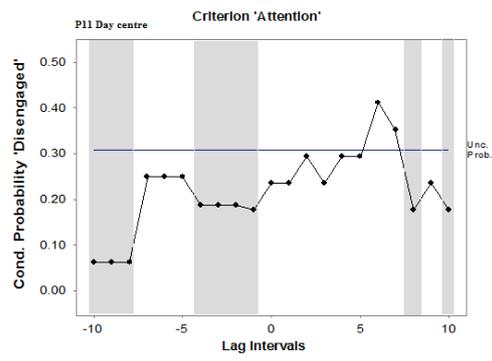
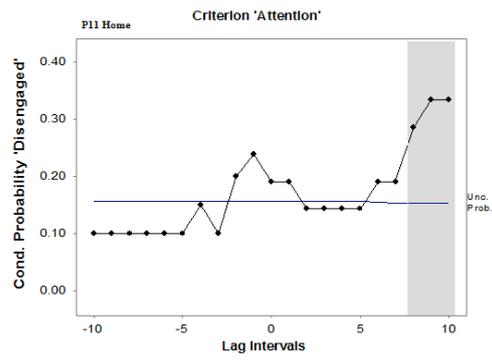
**Figures 11.1 Conditional probability of Disengagement 100 seconds before and 100 seconds after the onset of adult attention and the unconditional probability of disengagement. The shaded area indicates that the unconditional probability is significantly different from the conditional probability (absolute Yule's Q >0.3)**



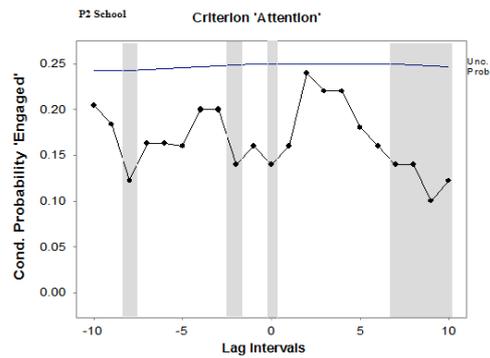
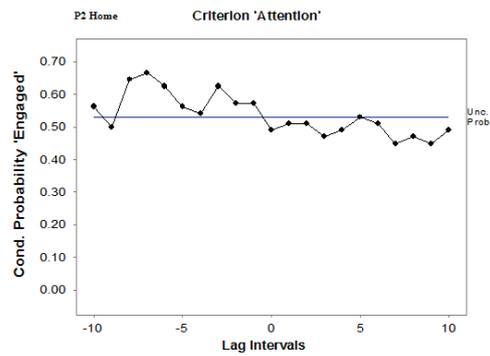
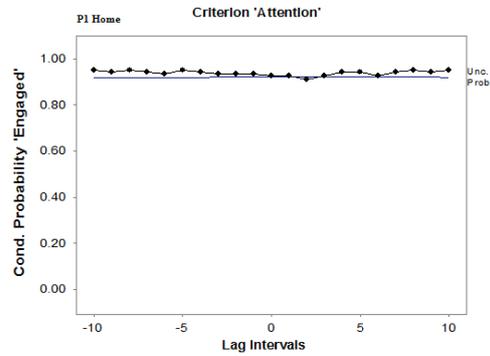


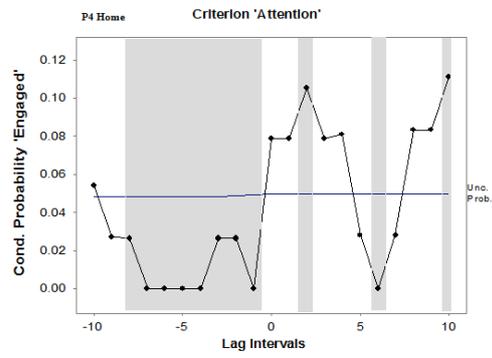
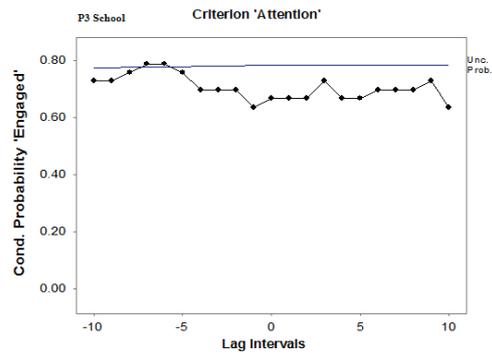
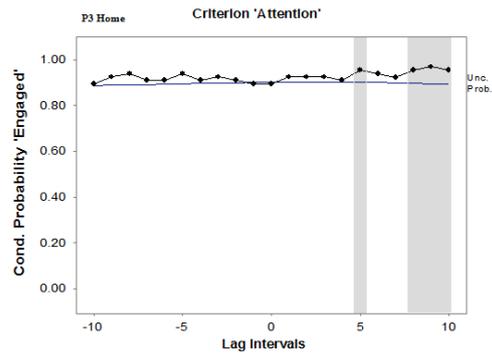


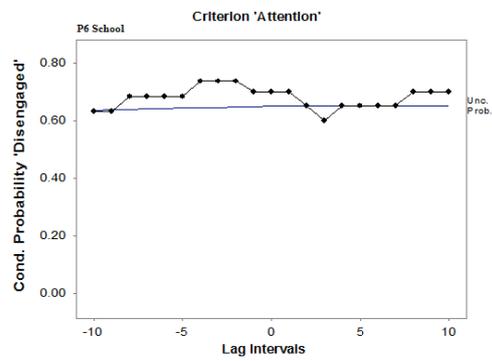
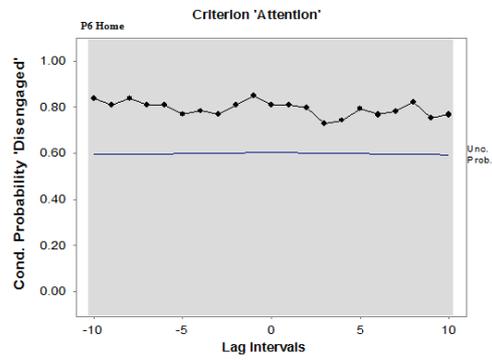
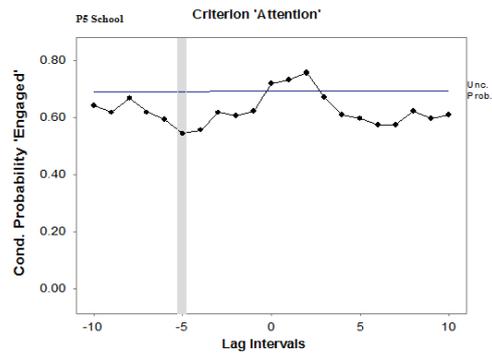
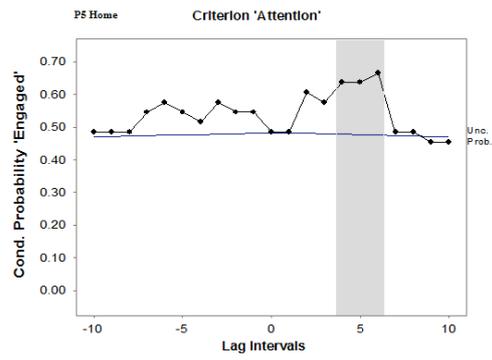


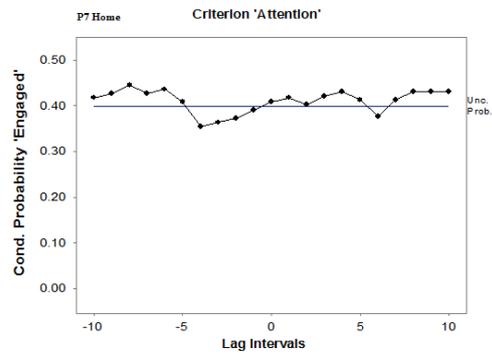
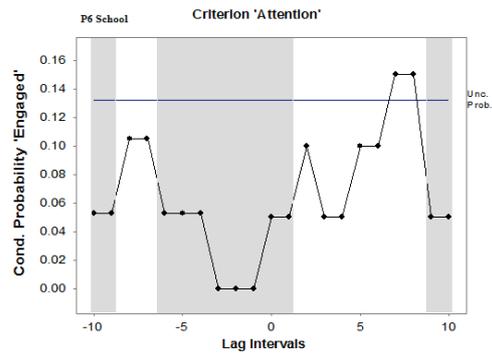
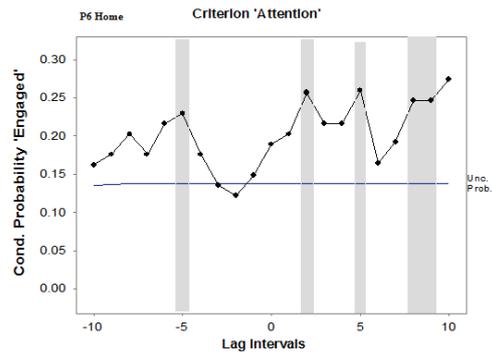


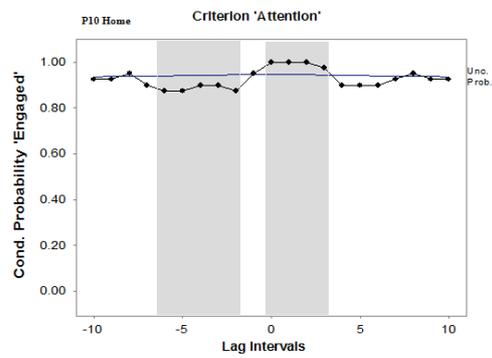
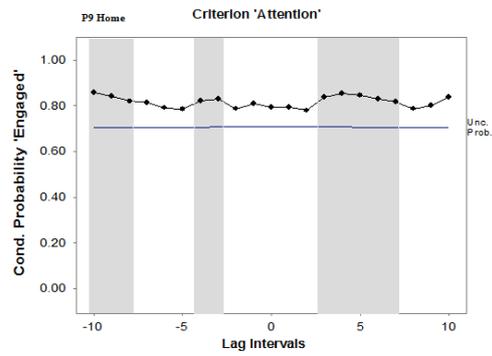
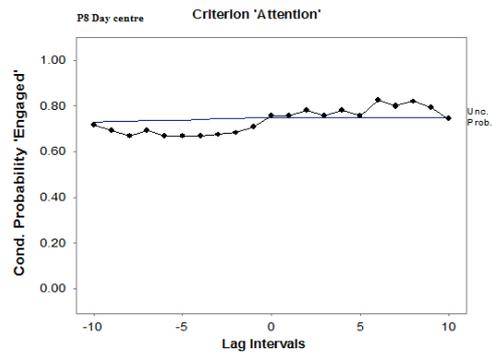
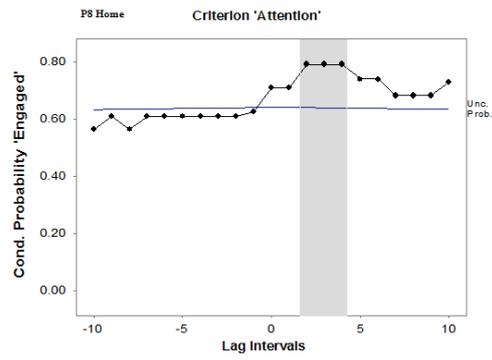
**Figures 11.2 Conditional probability of Engagement 100 seconds before and 100 seconds after the onset of Adult attention and the unconditional probability of Engagement. The shaded area indicates that the unconditional probability is significantly different from the conditional probability (absolute Yule's Q >0.3)**

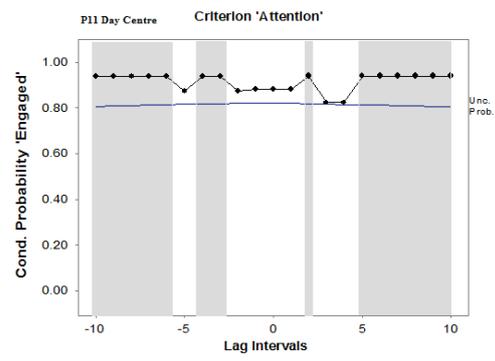
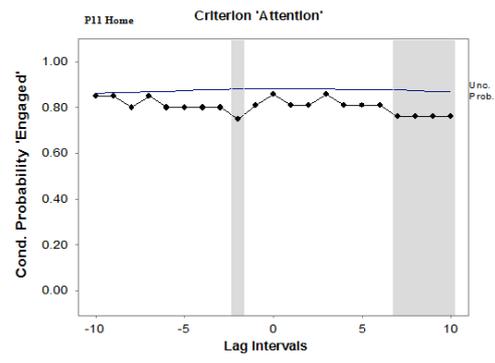




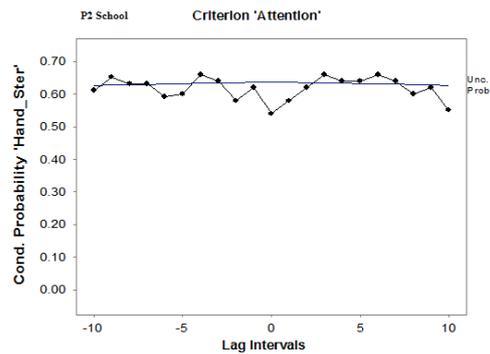
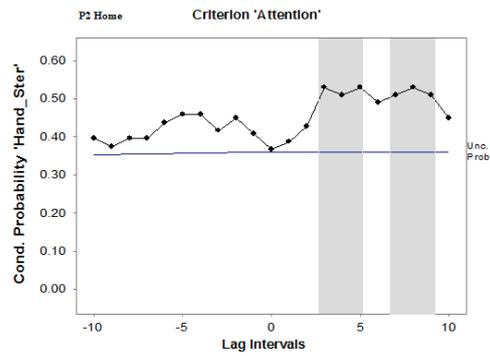
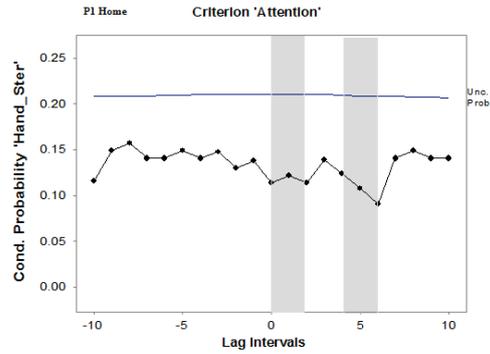


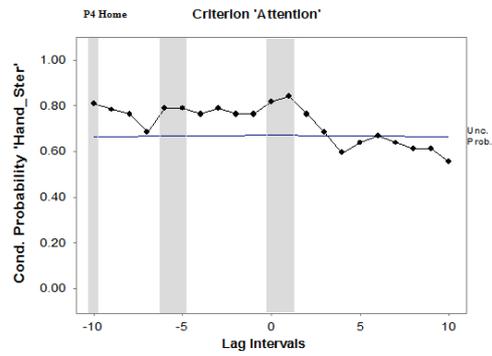
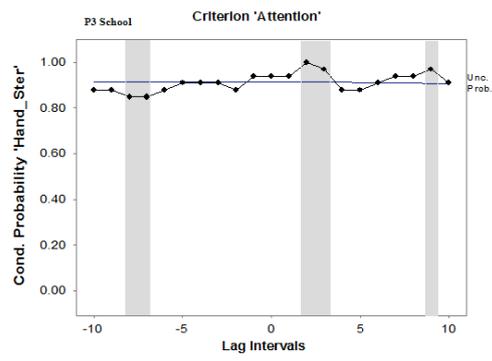
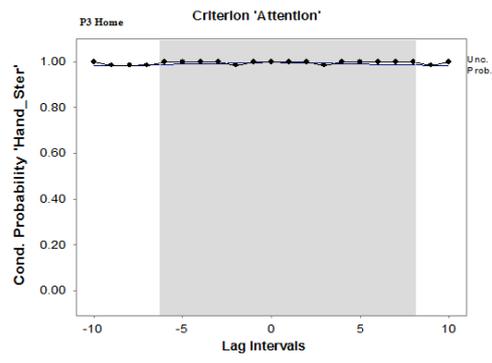


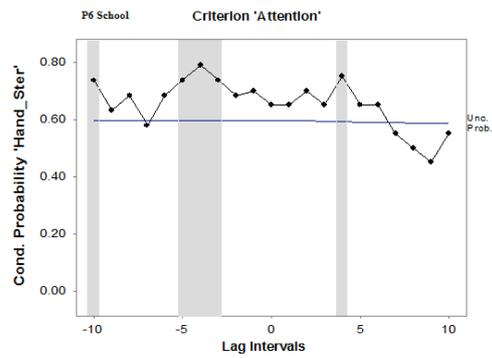
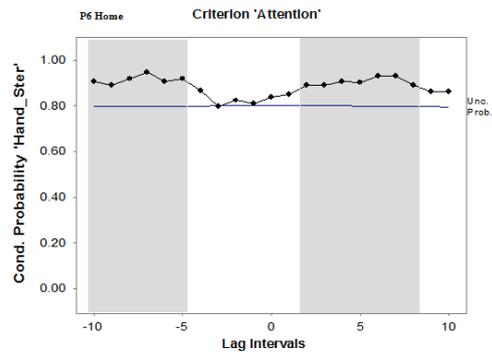
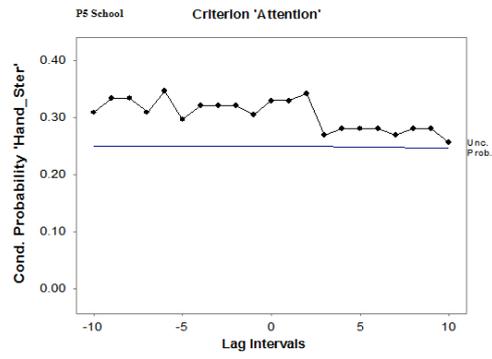
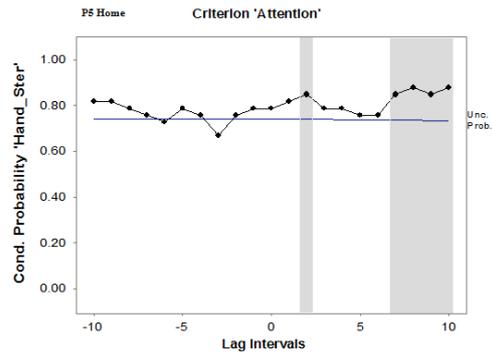


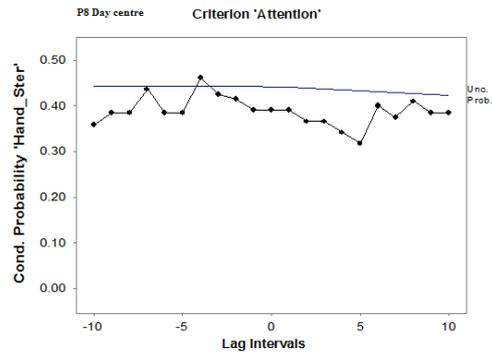
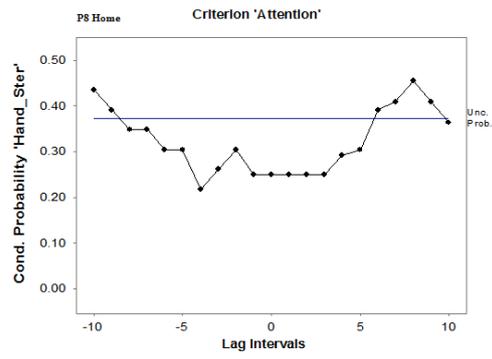
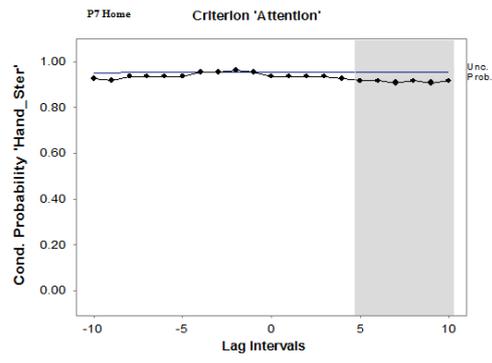


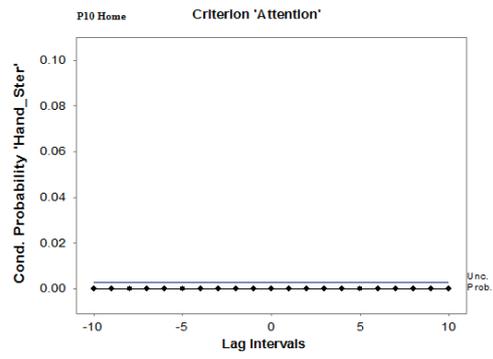
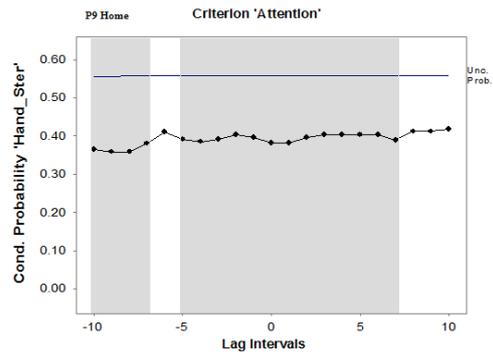
**Figures 11.3 Conditional probability of Hand stereotypes 100 seconds before and 100 seconds after the onset of Adult attention and the unconditional probability of Hand stereotypes. The shaded area indicates that the unconditional probability is significantly different from the conditional probability (absolute Yule's Q >0.3)**



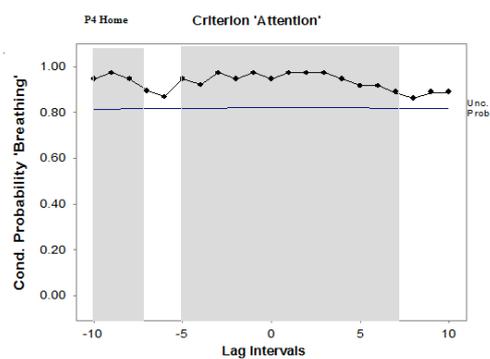
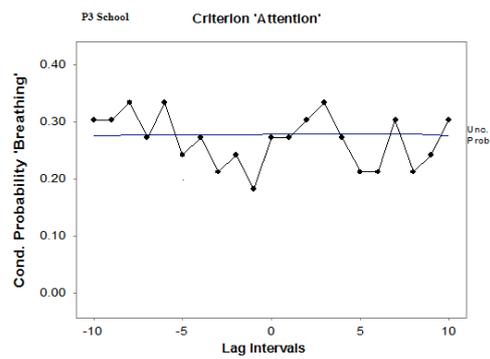
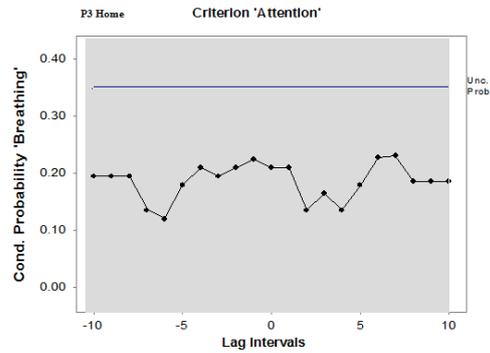




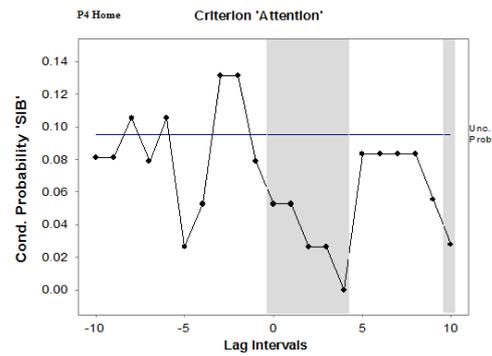
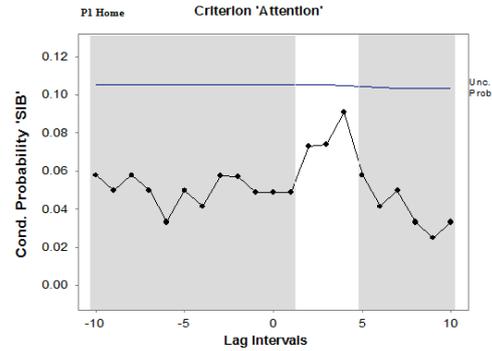


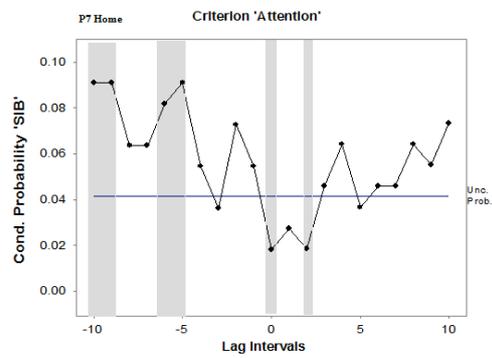
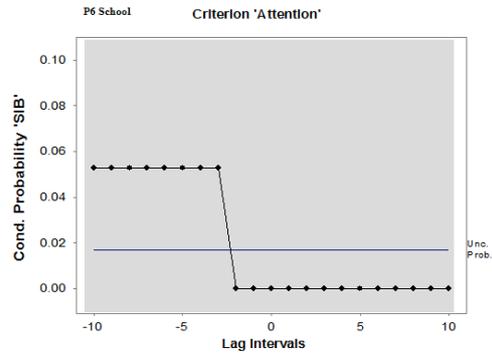
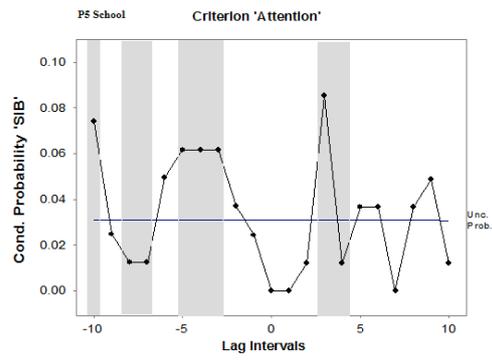
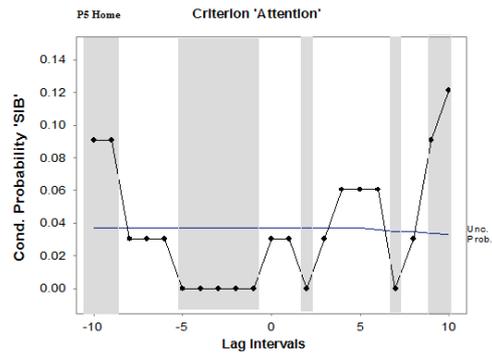


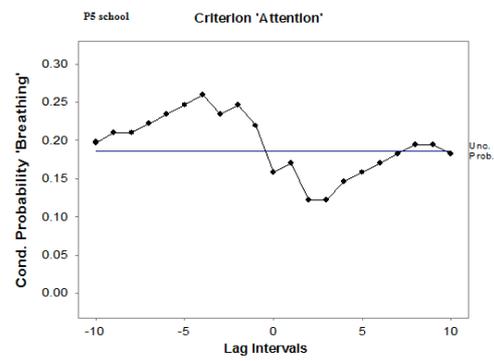
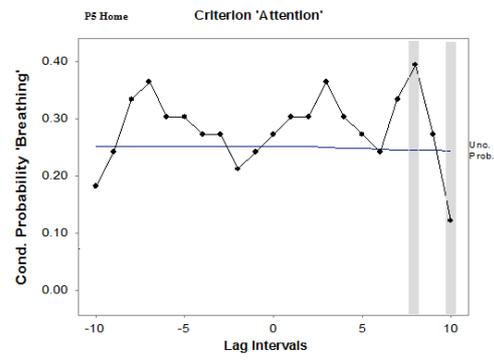
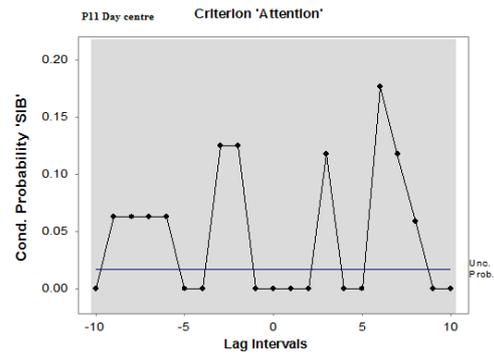
**Figures 11.4 Conditional probability of Breathing abnormalities 100 seconds before and 100 seconds after the onset of Adult attention and the unconditional probability of Breathing abnormalities. The shaded area indicates that the unconditional probability is significantly different from the conditional probability (absolute Yule's Q > 0.3)**

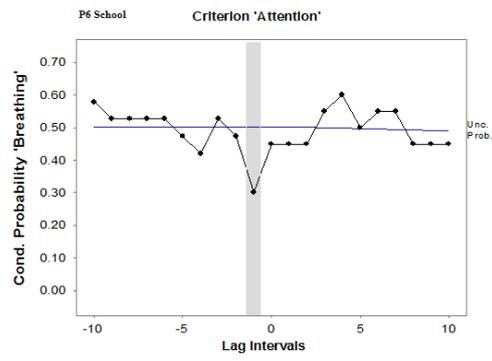
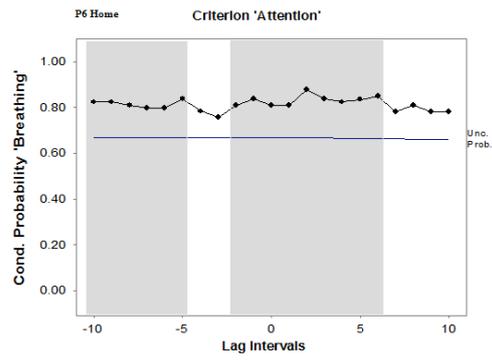


**Figures 11.5 Conditional probability of Self-Injurious behaviour 100 seconds before and 100 seconds after the onset of Adult attention and the unconditional probability of Self-Injurious behaviour. The shaded area indicates that the unconditional probability is significantly different from the conditional probability (absolute Yule's  $Q > 0.3$ )**









## CHAPTER 12

### GENERAL DISCUSSION

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#### **12.1 Introduction**

In the last two decades advanced genetic technologies and improved understanding of the psychological and emotional side of individuals with ID has led to an increased interest in the study of behavioural phenotypes in genetic syndromes with associated ID. This includes understanding the behavioural and emotional profile of RTT. Several medical and genetic treatments are under development. At the same time, there is an inadequate recognition of the psychological needs of the RTT population and their families. One of the features of RTT is a period of regression after an apparently normal development. This aspect of the syndrome has a severe impact on family well-being. Hence, it would seem important to provide support to the child and the family as early as possible to ensure optimal medical, social and emotional assistance, develop an individualised intervention and design a supportive environment for both the child and family.

Previous studies have reported that the child with RTT displays signs of developmental delay within the first few months of life. These may manifest as disturbances in general movements, the presence of unusual movements (e.g. excessive patting and waving of the hands) and a general lack of coordination. It is therefore important for the professional to recognise the symptoms of the syndrome as early as possible so as to give support to the families affected, increase knowledge of the syndrome and provide early intervention for the person with RTT to reduce the risk of the development of problem behaviours.

The three studies in this thesis were conducted with the aim of increasing understanding of the behavioural profile of RTT and the needs of families, so as to contribute to the identification of optimal support for those concerned. Factors associated with parental stress, mental health and positive perceptions were explored. In addition, organisation of the behavioural repertoire, responses to naturally occurring environmental stimuli and relationship between behaviour and environment were investigated through systematic observation.

### **12.2 Strengths and weakness of the study**

The sample of this study was recruited via a national database, the British Isles Rett Syndrome Survey, the UK and Ireland RTT database held in the Institute of Medical Genetics at Cardiff University. Although it was designed to be representative of RTT, the minority response rate means that it is not possible to determine its representativeness. However, all participants had a definitive diagnosis of RTT which was confirmed by genetic mutation in over 80% of the sample.

Moreover, this study included a large sample of adults. The majority of studies in the literature which include adults are clinical case studies. Very few explore the behavioural profile in adults using a sizeable sample. There is now evidence that girls with RTT survive into adulthood and that it is possible for the girls to regain some of the skills lost and learn new skills. In the long-term, researching developmental changes over time and focusing on adults could lead to an improvement in intervention and enhanced quality of life for this group.

Measurements used were well established with known psychometric properties. Some of these measures have been used in previous studies exploring RTT behavioural features, particularly the RSBQ, which was developed for such a purpose. Others

address aspects of the possible RTT phenotype that have not been described in the literature before using standardised assessment. Hyperactivity, self-injurious behaviour and mood are assessed using standardised measures that have been utilised in studies of the behavioural phenotype of individuals with other syndromes associated with profound/severe ID. In addition, the assessment of parental mental health and well-being used established measures that have been employed in studies of families whose with offspring with other syndromes.

Despite the numbers of measures used, which comprised two lengthy questionnaire packs, data collection was fairly complete, so the need for estimation of missing data was very limited. However, due to the large number of assessments used, the numbers of tests for statistical significance undertaken was large. A weakness was the failure to apply the Bonferroni test to adjust the critical region (by lowering the alpha level) to take into account of the number of tests performed. The decision not to apply the Bonferroni adjustment arose because of the increased likelihood of making type 2 errors when the critical region is reduced. Despite the sample being relatively large, RTT is a rare condition and sample size was low in some analyses, particularly those where the sample was divided according to age groups, severity, diagnostic and genetic mutation categories.

### **12.3 Summary of findings of the literature review on the behavioural phenotype of Rett syndrome**

Research on the behavioural phenotype of RTT has focused mainly on a single behaviour such as type and frequency of hand stereotypies, type of breathing abnormalities, or sleep disturbances and data from this study confirmed that these are behavioural features typically seen in this population. However, other behavioural

manifestations such as self-injury, autistic spectrum disorder, episodes of low mood and fear/anxiety, albeit relatively common, were by no means characteristic. Indeed, one of the interests in the existing literature is the differences/similarities amongst children with autism and RTT. There was an agreement that adults with RTT had the lowest rates of behavioural problems compared to adults with autism and the most interesting findings related to the social behaviour. Children with RTT appeared to enjoy social contact more and eye contact with the other person, smiling and looking at faces was observed in most of the cases with RTT. Individuals with RTT showed more behaviours associated with ASD and ID such as poor attention span, laughing and giggling without apparent reason and making non-speech noises, unresponsiveness to social stimuli and more repetitive behaviour. Hand stereotypies breathing abnormalities and sleep disturbances have been found sufficiently frequently in surveys to suggest that they are part of a RTT behavioural phenotype, reinforcing their presence in the essential diagnostic criteria.

Although the literature suggests a possible distinctive phenotype in RTT, the lack of well chosen matched control groups in existing studies prevents one from drawing definitive conclusions on which behaviours are specific to RTT, particularly in relation to such aspects as mood, overactivity, impulsivity, repetitive behaviours and self-injurious behaviours. Less than half of the studies included a control group and, where they did, comparison groups were not well matched in relation to participants' age, gender, adaptive skills and verbal abilities. In addition, studies which included a control group were restricted to behavioural features such as breathing abnormalities, autistic features and sleep disturbances. Although some early studies have reported hyperactivity and self-injurious behaviour in RTT, these were descriptive studies without an adequate comparison group to establish whether these behaviours are a

characteristic of RTT as opposed to a common problem of individuals with severe/profound ID.

There have been some studies which adopted a longitudinal design, however most of the research conducted to date does not explore the developmental trajectory of the syndrome and age related changes. The little research that has explored variation across age did not have robust methodology, in particular studies lacked control groups and did not use appropriately validated measures. Hence, it is difficult to interpret the results from these studies.

Cognitive and communication skills were the behavioural aspects most commonly reported as these are the areas mostly impaired (together with the motor skills) in RTT. Eye pointing, stereotypies, facial expression, walking towards desired items, body movements, pushing away and reaching were some of the communicative behaviours reported in the studies. Despite the importance of communication and language abilities, to date, there does not seem to be a communication mode or measurement tool adapted for this population, in order to allow effective assessment of communication and learning abilities and effective interaction with the environment.

The findings from the review point towards two conclusions. First, studies agreed that children/adults with RTT function in the severe/profound ID level after the regression stage and analysis of the forms and function of communicative acts has reported no consistent results. The argument in the literature is whether the RTT girls/women experience a true dementia or a cognitive arrest at the point of language and motor regression (Van Acker 2010). Fontanesi and Haas (1988) indicated that the girls experience a stagnation of function rather than a dementia and other studies have not found evidence of dementia in this population. Generally, there was little evidence of intentional communication in the studies reviewed. Second, in the majority of

studies, subjects were assessed using traditional standardised instruments requiring fine motor skills, in particular the hands, known to be impaired in the disorder. RTT is characterised by loss of acquired language, communication and motor abnormalities, loss of functional hand skills and delayed response latency. Thus traditional methods of cognitive assessment are often inadequate for individuals with RTT and often problematic due to the severe motor and verbal abilities. It is possible that poor results were interpreted as cognitive impairment, without taking sufficient consideration for the individuals' other difficulties.

#### **12.4 Characterising the behavioural phenotype of Rett syndrome. The national survey**

Analysis of the cross sectional data of this study did not find any significant trend in the behavioural phenotype across age groups, with the exception of level of activity and mood. However, the cross sectional nature of the study did not allow for definitive conclusions about developmental changes over time, as longitudinal effects could not be separated from cohort effects.

Adaptive behaviour was assessed. There was variation between individuals and across age groups but the great majority showed a profound level of delay. The older group performed better in the daily living skills and motor skills domains, which could suggest individuals with RTT may regain or learn some skills lost during the regression stage as they grow older, or that cases with a more severe phenotype do not survive into adulthood. Hand stereotypies were reported in all individuals, which suggest that the behaviour is typical of the syndrome. Moreover, results from the RBQ confirmed that hand stereotypies were 5 times more frequent than other stereotypies. Findings from the RSBQ did not differ across groups. Autistic features, self-injurious behaviour and

impulsivity were not very common in this sample. In particular, autistic features were measured among the children using the DBC-ASA group and only 29% of the participants had a score of clinical significance, suggesting that it does not occur in RTT more commonly than among other individuals with ID. However, autistic features were linked to a less severe phenotype, higher RSBQ scores and SIB.

SIB was more frequent in those participants with a more severe clinical phenotype and in those with higher scores on the DBC and RSBQ. SIB was also related to impulsivity. The link between SIB and impulsivity has been established in other syndromes, such as Cornelia de Lange, Prader Willi syndrome, Lowe syndrome and Fragile X syndrome (Arrow et al. 2011). Further studies are required to explore SIB in RTT, in particular looking at the role neurological function and the link between behaviour and environment.

Although the descriptive data here may suggest some variability across genetic mutations, the results need to be interpreted with caution due to the very small number of cases in each group. Although previous studies have described some differences between the type of mutation, with a milder phenotype being associated with behaviours relating to anxiety and changes of mood and a severe phenotype being associated with behaviours related to the hands and daytime sleep, it is difficult to establish relationships due to the fact that RTT is a rare condition and subjects in each group are quite small (Robertson et al. 2006) and due to differing methodologies and the means by which to measure severity.

## **12.5 A comparative study on hyperactivity, depression, self-injurious behaviours and repetitive behaviour in Rett syndrome and individuals with different genetic syndromes**

In this study the behaviour of the RTT group was compared with a group of individuals with different genetic syndromes, matched for age, gender, adaptive skills and language abilities. One of the many challenges in the behavioural phenotype field is the understanding of the differences and similarities amongst individuals with different genetic syndromes and indeed individual differences within the same syndrome. To my knowledge, this is the first study to employ a well-matched comparative design. The RTT sample was only compared to the control group in relation to the MIPQ, AQ, RBQ and self-injurious behaviours as data from the RSBQ, VABS and DBC were not available for the control group.

The comparison study provided some evidence that although impulsivity, overactivity, low mood and self-injurious behaviours are sometimes reported in RTT, these are not typical of RTT. Although both groups had a similar level of mobility, it is possible that additional physical difficulties typical of RTT, such as apraxia, scoliosis and inability to use the hands functionally may have influenced the level of activity found (e.g., the control group were more able in terms of feeding ability). Factors such as the severity of the clinical phenotype and mobility were found to be associated with a higher level of impulsivity and overactivity in the RTT group. Furthermore, although SIB was reported in some of the participants, it was clear that its frequency of occurrence when compared to the control group was not sufficient for it to be included in the RTT phenotype.

A significant finding was that repetitive hand stereotypies were distinctive of RTT compared to the control group as a whole, but not when compared only to individuals

with Angelman syndrome. Although the behaviour was reported in both syndromes, it could be that a specific topography of the behaviour is associated with a specific syndrome. There are no other studies to my knowledge that compare specific behavioural features associated with RTT, such as hand stereotypies, with a control group (apart from children with autism). Research is needed to explore and compare the frequencies and topographies of hand stereotypies in RTT and Angelman syndrome. Such research should include qualitative observation. Arrow et al. (2011) found that different topographies of SIB were associated with different genetic syndromes. Thus it may well be the case that the hand stereotypies of individuals with RTT are topographically different from the hand stereotypies found in Angelman syndrome.

### **12.6 Psychological health and well-being in families with a daughter with Rett syndromes**

Studies exploring the psychological dynamics of family caring for children/adults with RTT are rare. There are only two studies to my knowledge that have looked at stress, family adjustment and mental health. None of the studies explored the impact of stress in those families caring for an adult with RTT. In addition no studies were identified that looked at the positive perception of caring for a child/adult with severe physical and intellectual disabilities. Growing evidence suggests that positive experiences are often reported by parents of children with ID and that positive perception of having a child with ID may serve as a coping strategy.

The aim of the family study was to investigate the impact that severity of clinical and behavioural presentation has on the family. Consistent with other studies on family stress, the severity of the behavioural presentation and not the severity of the clinical phenotype was found to have an impact on family stress. Stress, anxiety and depression

were found to be related to increased severity in areas such as mood, fear/anxiety, body rocking and expressionless face. One hypothesis of the relationship between maternal mental health and increased severity in repetitive movement, such as face grimacing and tongue movements, is that they are associated with neurological severity of the condition and thus the mother may see these behaviours as embarrassing and not acceptable. However, what was highlighted in the study was that families with a daughter with RTT experienced relatively modest stress and reported high positive gain and affect. For example, compared to a study exploring the psychological well-being of parents with children with Angelman syndrome, Cornelia de Lange and Cri du Chat syndrome, parents of children with RTT reported less stress and depression. This may be explained by the fact children with RTT display less severe challenging behaviours and physical aggression is rarely reported in RTT.

Older parents in general showed a lower level of stress compared to younger ones, indicating that parents tend to adapt or, again, that there is a 'healthy survivor' effect with individuals living longer being those who impart less stress. It could be possible to hypothesise a link between adaptation and positive perceptions and feelings. For example, perception of progression in skills were found to be linked to high positive experience. This was one of the first studies to measure positive perception and experience in parents with a child/adult with RTT and further studies are needed to explore how these and other variables may support positive adaptation and psychological well-being. One of the limitations of this study was the absence of a comparison data for the family study. Further studies are recommended including a comparison group.

## **12.7 A longitudinal study of the behavioural phenotype of Rett syndrome and family psychological health and well-being**

The longitudinal study had the aim to address developmental changes in RTT and to explore positive and negative experiences in the family over time. Longer follow-up would have been desirable. However, due to time constraints, the participants were followed up after only 16 months.

The behavioural features of the group were found to be stable over time and although some trends were highlighted in the analysis, results must be treated with caution due to the small sample size and the short follow-up period. In general, the trend of the analysis suggested a decrease in behavioural problems and a decrease in mood/interest in the adult population. In order to gain more significant insights into developmental change, a bigger sample size is required and a longer follow-up period is necessary.

Results of the family study were consistent with the cross-sectional study. The child behavioural problems were associated with maternal stress, anxiety and depression. Using linear regression analysis, it was possible to analyse the relationship between increased behavioural problems and maternal stress. The results suggested that increased severity of behavioural problems is linked to worse maternal psychological well-being.

## **12.8 The behavioural observations. A descriptive study of the behavioural profile of a group of girls/women with Rett syndrome**

The behavioural observation stage was seen as an important part of the study. As RTT is a rare genetic syndrome, the behavioural and emotional manifestations may not be described in standardised scales. Direct observation can be useful to describe behaviour that may not be measured within established assessments. It can be sensitive to qualitative differences in behaviour across participants within the same syndrome.

Behaviours most frequently seen in the group who were observed included: hand stereotypies, breathing abnormalities and self-injurious behaviours. Other stereotypies such as bruxism, body rocking and tongue protrusion were also often observed; however due to poor inter-rater reliability the category was excluded from analysis. Hand stereotypies were very frequent for the vast majority of the participants. However, analysis suggested that these stereotypies were less frequent when the girls/women were engaged in another activity using the hands. Breathing abnormalities were observed in the younger girls. The behaviour tended to attract adult attention, mostly in the form of prevention (e.g. telling the child to breath).

The observation study suggested that the self-injurious behaviour could be maintained by adult attention (to gain attention and to escape attention) in 4 of the girls. However, the sample size in the observation study was quite small and self-injurious behaviours were observed in only half of the sample. As a link between SIB and environmental conditions was suggested for some of the girls, it would seem important to consider operant conditioning as a possible factor influencing such behaviour in girls/women with RTT. It is also thought that the mechanism responsible for pain processing is disrupted in RTT. MeCP2 has been reported to have a key role in pain plasticity in the mouse model. Decreased pain sensitivity is often reported in RTT, thus

indicating a disruptive mechanism in pain signalling. However, the association between decreased pain signalling and increased SIB has not been investigated to date and so further studies are required in this population. Moreover, as already reported, SIB was certainly not found to be characteristic of RTT and to occur less frequently than in some other syndromes associated with severe/profound ID. Hence, a generalised effect on all individuals with the syndrome would appear unlikely.

### **12.9 Implications and recommendation for future research**

This was one of the largest surveys which has explored behaviours such as level of mood, hyperactivity and self-injurious behaviour, that have not been assessed systematically in this group before. In addition, the findings from the RTT group were analysed using a closely matched comparison group with similar ability and level of ID.

Although there were a number of limitations of this study, which included the cross sectional design of the first study and the number of participants for the longitudinal study, it has provided some new insights on how to understand the behaviour of girls with RTT better and how the family cope and adapt over time to the challenges they face.

Findings from this study have a number of important implications. The first is to translate the understanding of the behavioural profile of girls with RTT so that this knowledge helps parents and carers and can lead to better targeted and earlier individualised intervention for the individual and their family. One of the findings of the observational study was that breathing abnormalities attracts adult attention in the form of telling the child to breathe. The breathing abnormalities can cause great concern and anxiety in parents and often are confused with epileptic seizures. Thus it is important to provide support to the families and the child as soon as possible during regression, to

give optimal medical, social and emotional assistance. Increasing parents' knowledge about breathing abnormalities and epilepsy could lead to better quality of life for the girls affected. Adjusting the environment and the use of calming strategies, such as using music therapy has been shown to be effective with some girls. Music therapy has been used successfully to reduce behavior such as hyperventilation or to increase in hand use (Wesecky 1986; Wylie 1996) and can be used as a sources of motivation to reduce problem behaviours (Zappella 1986). Although the family study indicated that most of the mothers did not experience high level of stress, anxiety and depression, early intervention for parents with high level of anxiety, depression and stress is necessary, in particular help that target symptoms specific to RTT, e.g. mood changes, breathing abnormalities and epileptic seizure. A key role in the support for families is played by the multidisciplinary clinics run specifically for families and children/adult with RTT. The clinics are formed by experts in RTT such as specialists in genetics, speech and language therapists, physiotherapists, specialists in epilepsy and dieticians. The aim of the clinics is to provide medical and psychological support for the families and the individual with RTT with problems related to the syndrome.

Another important point highlighted in this study is the need for the development of measures tailored to this population. One of the findings from the literature review was that assessments and tests administered to the RTT sample were not adapted for this particular group. There is only one measure developed to date to assess RTT specific characteristics, the RSBQ. However, the scale is in need of an update. In fact, the scale was developed before the Hagberg et al. (2002) and Neul et al. (2010) diagnostic criteria were developed. Although the scale has good psychometric properties, it has only been validated with children (albeit that it has been used in a number of studies which have included adults, including this one). Most cognitive assessments require the

use of the hands to hold, reach or point, skills that the RTT girls lose during the regression stage. Severe motor difficulties, apraxia and severe communication difficulties limit the way girls with RTT can express themselves and also how they respond to standardized assessment methods. These types of assessments are not adequate for the RTT group as they lead to an underestimation of the girl abilities. More recently, eye-gaze tracking technology has become a popular tool, as it is a way by which girls with RTT can communicate and it can be an important tool for assessing how much the girls can understand, discriminate stimuli in the environment and intend to communicate. The work by Baptista et al. (2006) is a good example of how the use of eye-tracking technology can help to understand the cognitive abilities of girls with RTT. The study highlighted that the participants were able to discriminate familiar objects and to follow verbal instructions. Experiments conducted in Italy (Fabio and Giannatiempo 2009) confirmed the findings that individuals with RTT are able to respond to simple verbal requests (i.e. look at the dog), thus highlighting the fact that eye tracking technology could be a valid instrument to assess cognitive abilities in girls affected by severe/profound motor and ID.

The study of the RTT behavioural phenotype and comparison to other genetic syndromes will enhance our understanding of the RTT and facilitate the design of individualised therapeutic programmes targeting particular behaviours. Until now, a focus of research has been on describing the characteristics of the hand movements. There is a need for more studies looking at early intervention on reducing hand stereotypies and increasing functional hand skills.

Few studies have investigated the effect of behavioural intervention in reducing hand stereotypies and increasing functional use of the hands. Piazza et al. (1993) examined the effects of prompting and reinforcement on the self-feeding skills of five

girls with RTT. The intervention consisted of a three step prompting procedure: scoop the food onto the spoon, bring the food to the mouth and place the food in the mouth. Results showed that all of the girls improved their self-feeding skills and follow-up data indicated that the girls maintained the skills over time. Although this study did not provide any data on generalisation of hands skills in general and the sample size was small, it provided some evidence that it is possible to teach functional skills to this population using a self-reinforcing situation (eating). Some earlier studies have explored the use of elbow orthosis and hand splints in children with RTT. Although some successes have been reported (e.g. Shape 1992), benefits of the use of hand splints and elbow orthosis cannot be generalise to the Rett population (Tuten and Miedaner 1989). In addition there is no evidence for maintenance of the reduction of hand stereotypies, in fact the stereotypies usually appear again after the splints are removed.

The findings of this study highlighted that hand stereotypies occurred less in some of the participants who were engaged in activities involving the use of the hands. Although reduction in hand stereotypies were not observed in all participants, the findings from this study might have implications for future early intervention. For example intervention targeted for the individual using Active Support may help to focus on specific skills and would help to set frequent and specific opportunity for the individual.

Individuals with RTT and their family have specific needs and it is important to take the individuals needs into consideration during early intervention programmes. Music therapy has been used with individuals with RTT since the condition was described in the literature and Dr Andreas Rett recommended it as a tool to help the girls. Music therapy has been found to induce positive response in girls and adults with the syndrome. Studies have shown how music promotes and motivates their desire to

interact and communicate with their surroundings as well as develops their cognitive, affective, sensori-motor and physical skills. It has been suggested that the use of instruments can be a motivating way for children to purposefully improve hand use, increase grasping/holding, decrease stereotypical movements and reduce hyperventilation (Wigram 1997, Wigram and Lawrence 2005). Although these studies have reported some improvements in hand use and reduction in anxiety, these are temporary outcomes and it is yet to be established whether the use of music is beneficial to the Rett population in the long term. There have been only a few studies that provide evidence on early behavioural intervention in RTT and more evidence is needed to demonstrate validity of functional skills teaching programmes in the real world together with maintenance and generalisation of the intervention over time. Designing better evaluation strategies to determine the functional significance of movements and vocalisations and be aware of multiple factors affecting the behaviour of individuals with RTT could increase success in teaching functional skills in this population (Weyemer et al. 1993).

## References

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AAIDD, Intellectual Disability: Definition, Classification, And Systems Of Supports (11<sup>th</sup> Edition) 2010.

Abbeduto, L., Seltzer, M.M. and Shattuck, P. (2004). Psychological well-being and coping in mothers of youths with Autism, Down syndrome, or Fragile X syndrome. *American Journal on Mental Retardation*, 109, 237 – 254.

Aicardi, J. (1998). The Etiology of Developmental Delay. *Seminars in Pediatric Neurology*, 5, 15-20.

American Psychiatry Association (2000). *Diagnostic and statistical manual of mental disorders*, (4<sup>th</sup> Edition) Washington, DC, American Psychiatric Association,

Amin R.E., Veyver I.B., Wan M., Tran C.Q., Franckle, U. and Zoghbi H.Y. (1999). Rett syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG – binding protein 2. *Nature Genetics*, 23, 185-187.

Archer, H., Evans J., Leonard H., Colvin L., Ravine D., Christodoulou J., Williamson S., Charman T., Bailey M.E., Sampson J., De Klerk N. and Clarke A. (2007). 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, 148-52.

Archer, H. (2007). Clinical and molecular investigation of Rett syndrome and related disorders, Unpublished MD Thesis.

Arron, K., Oliver, C., Hall, S., Sloneem, J., Forman, D. and Mcclintock, K. (2006). Effects of social interaction on pragmatic communication and self-injurious behavior in Cornelia de Lange syndrome, *American Journal on Mental Retardation*, 111, 184 – 192.

Arron K., Oliver, C., Moss, J., Berg, K. and Burbridge, C. (2011). The prevalence

and phenomenology of self-injurious and aggressive behaviour in genetic syndromes. *Journal of Intellectual Disability Research*, 55, 109-120.

Arvio, M. and Sillanpaa, M. (2003). Prevalence, aetiology and comorbidity of severe and profound intellectual disability in Finland. *Journal of Intellectual Disability Research*, 47, 108-112.

Bahi-Buisson N., Nectoux J., Rosas-Vargas H., Milh M., Boddaert N., Girard B., Cances C., Ville D., Afenjar A., Rio A., He.Ron D., N'Guyenmorel M., Arzimanoglou A., Philippe C., Jonveaux P., Chelly J. and Bienvenu T. (2008). Key clinical features to identify girls with CDKL5 mutations. *Brain*, 131, 2647-2661.

Bailey, D. (2007). Introduction: family adaptation to intellectual and developmental disabilities. *Mental Retardation and Developmental Disabilities*, 13, 291 – 292.

Bakeman, R. and Gottman, J.M. (1997). Observing interaction. An introduction to sequential analysis, Cambridge University Press, 2<sup>nd</sup> Edition.

Baker, B.L., McIntyre, L.L., Blacher, J., Crnic, K., Edelbrock, C. and Low, C. (2003). Pre-school children with and without developmental delay: behaviour problems and parenting stress over time. *Journal of Intellectual Disability Research*, 47, 217 – 230.

Baptista, P. M, Mercante, M. T, Macedo E. C. and Schwartzman, J. S. (2006). Cognitive performance in Rett syndrome girls: a pilot study using eye-tracking technology. *Journal Of Intellectual Disability Research*, 50, 662-666.

Bashina, V.M., Simashkova, N.V., Grachev, V.V. and Gorbachevskaya, N.L. (2002). Speech and motor disturbances in Rett syndrome, *Neuroscience and Behavioral Physiology*, 32, 323-327.

Basile, E., Villa, L., Selicorni, A. and Molteni, M. (2007). The behavioural phenotype of Cornelia de Lange syndrome: a study of 56 individuals. *Journal of Intellectual Disability Research*, 51, 671–681.

Bassett A.S., Chow, E.W.C., Husted, J., Weksberg, R., Caluseriu, O. Webb, G.D.

and Gatzoulis, M.A. (2005). Clinical features of 78 adults with 22q11 deletion syndrome. *American Journal of Medical Genetics*, 138A, 307-313.

Bakeman R, McArthur D, Quera V. (1996). Detecting group differences in sequential association using sampled permutations: Log odds, kappa, and phi compared. *Behavioral Research Methods, Instruments, and Computers*. 28, 446–457.

Bakeman, R., Robinson, B. and Quera, V. (1996). Testing sequential association: Estimating  $p$  value using sample permutations, *Psychological Methods*, 1, 4 – 15.

Bakeman, R., Gottman, J.M. (1997). *Observing interaction: An introduction to sequential analysis* (2nd ed.) Cambridge, UK: Cambridge University Press.

Bayley, N. (1969). *Bayley Scale of Infant Development*. New York, The Psychological Corp., D., Fyfe, S., P

Bebbington, A., Anderson, A., Ravine ineda, M., De Klerk, N., Ben-Zeev, N., Yatawara, N., Percy, A., Kaufmann, W.E., and Leonard, H. (2008). Investigating genotype-phenotype relationships in Rett syndrome using an international dataset. *Neurology*, 70, 868-875.

Berg, K., Arron, K., Burbidge, C., Moss, J. and Oliver, C. (2007). Carer-reported contemporary health problems in people with severe and profound intellectual disability and genetic syndromes. *Journal of Policy and Practice in Intellectual Disabilities*, 4, 120- 128.

Bergstroem-Isacsson, M. and Witt –Engerstrom, I. (2001). Music and the Rett disorder: The Swedish Rett Center Survey. *Nordic Journal of Music Therapy*, 10, 43-53.

Bergstrom-Isacsson M. and Witt –Engerstrom, I. (2007). Autonomic responses to music and vibroacoustic therapy in Rett syndrome: a controlled within-subject study. *Nordic Journal Of Music Therapy*, 16, 42-59.

Bernard, H.R. (2000) *Social Research Methods*. London: Sage

Berryman D. and Barrett L. (2002). Hand management in Rett syndrome. *Rett*

syndrome Association of Australia (RSAA) Newsletter July 2002.

Bird A. (2007). "DNA Methylation" In Head E. (Eds.). Epigenetics. Concept, theories, paradigms and mechanisms, THE BIOMEDICAL And LIFE SCIENCE COLLECTION, HENRY STEWARD TALKS Ltd, London  
(Online At [Http://Hstalks.Com/Bio](http://Hstalks.Com/Bio)).

Blagowidow, N., Kline, A.D. and Audette, L. (2005). Puberty and adolescence in Cornelia de Lange syndrome. *Proceedings of Greenwood Genetic Center*, 24, 175-176.

Boer, H. and Clarke, D. (1999). Development and behaviour in genetic syndromes: Prader-Willi syndrome. *Journal of Applied Research in Intellectual Disabilities*, 12, 296-301.

Breau, L.M., Mcgrath, P.J., Camfield, C.S. and Finley, G.A. (2002). Psychometric properties of the Non-Communicating Children's Pain Checklist-Revised. *Pain*, 99, 349-357.

Brereton, A.V., Tonge, B., Mackinnon, A.J. and Einfeld, S.L. (2002). Screening young people for autism with the Developmental Behavior Checklist. *Journal of American Academy of Child and Adolescent Psychiatry*, 41, 1369-1375.

Budden, S., Meek, M. and Henighan, C. (1990). Communication and oral-motor function in Rett syndrome. *Developmental Medicine and Child Neurology*, 32, 51-5.

Budden S.S., Dorsey H.C. and Steiner R.D. (2005). Clinical profile of a male with Rett syndrome. *Brain & Development*, 27, S69-S71.

Bumin, G., Uyanik, M., Kayihan, H., Duger, T. and Topcu, M. (2002). The effect of hand splints on stereotypic hand behavior in Rett's syndrome. *Turkish Journal of Pediatric*, 44, 25-9.

Burbidge, C., Oliver, C., Moss, J., Arron, K., Berg, K., Furniss, F., Hill, L., Trusler, K. and Woodcock, K (2010). The association between repetitive behaviours, impulsivity and hyperactivity in people with intellectual disability. *Journal of Intellectual Disability Research*, 54, 1078 – 1092.

Burford, B. and Trevarthen, C. (1997). Evoking communication in Rett syndrome: comparisons with conversations and games in mother-infant interaction. *European Child Adolescent Psychiatry*, 6 Suppl 1, 26-30.

Burford B., Kerr A.M. and Macleod H.A. (2003). Nurse recognition of early deviation in the development in home videos of infants with Rett disorder. *Journal of Intellectual Disability Research*, 47, 588-596.

Burford B. (2005). Perturbations in the development of infants with Rett disorder and the implications for early diagnosis. *Brain & Development*, 27, S3-S7.

Carter, P., Downs, J., Bebbington, A., Williams, S., Jacoby, P., Kaufmann, W.E. and Leonard, H. (2010). Stereotypical hand movements in 144 subjects with Rett syndrome from the population-based Australian database. *Movement Disorders*, 25, 282-288.

Cass, H., Reilly, S., Owen, L., Wisbeach, A., Weekes, L., Slonims, V., Wigram, T. and Charman, T. (2003). Findings from a multidisciplinary clinical case series of females with Rett syndrome. *Developmental Medicine and Child Neurology*, 45, 325-37.

Cattell, P. (1940). *The Measurement of Intelligence of Infants and Young Children*. New York: Psychological Corporation.

Chahrour, M. and Zoghbi, H.Y (2007). The story of Rett syndrome: From clinic to neurobiology. *Neuron*, 56, 422-437.

Chahrour, M., Jung, S.Y., Shaw, C., Zhou, X., Wong, S.T.C., Qin, J. and Zoghbi, H.Y (2008). MeCP2, a key contributor to neurological disease, activates and represses transcription. *Science*, 320, 1224-1229.

Charman, T., Neilson, T. C., Mash, V., Archer, H., Gardiner, M. T., Knudsen, G.P., McDonnell, A., Perry, J., Whatley, S.D., Bunyan, D.J., Ravn, K., Mount, R.H., Hastings, R.P., Hulten, M., Orstavik, K.H., Reilly, S., Cass, H., Clarke, A., Kerr, A. M. and Bailey, M.E. (2005). Dimensional phenotypic analysis and functional categorisation of mutations reveal novel genotype-phenotype associations in Rett syndrome. *European Journal of Human Genetic*, 13, 1121-30.

Chen, W., Chang, Q., Lin, Y., Meissner, A., West, A.E., Griffith, E.C., Jaenisch, R. and Greenberg, M.E. (2003). Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science*, 302, 885-889.

Cirignotta, F., Lugaresi, E. and Montagna, P. (1986). Breathing impairment in Rett syndrome. *American Journal of Medical Genetic*, Suppl. 1, 167-73.

Clarke, A., Schanen, C. and Anvret, M. (2001). Towards the genetic basis of Rett syndrome In: Kerr, A. and Witt Engerstrom, I., (2001) *Rett Disorder and the developing brain*, Oxford University Press, 27-55.

Clayton-Smith, J., Watson, P., Ramsden, S., and Black, G. (2000). Somatic mutation in *MECP2* as a non-fatal neurodevelopmental disorder in males. *Lancet*, 356, 830-832.

Cobb, S., Guy, J. and Bird, A. (2010). Reversibility of function deficit in experimental model of Rett syndrome. *Biochemical Society Transactions*, 38, 498-506.

Coleman, M., Brubaker, J., Hunter, K. and Smith, G. (1988). Rett syndrome: A survey of North American patients. *Journal of Mental Deficiency Research*, 32, 117-24.

Cook, J.A., Lefley, H.P., Pickett, S.A. and Cohler, B. (1994). Age and family burden among parents of offspring with severe mental illness. *American Journal of Orthopsychiatry*, 64, 435 – 447.

Coplan, J. (1983). *The Early Language Milestone Scale*. Tulsa: Modern Education Corporation.

Cornish, K., Scerif, G. and Karmiloff-Smith, A. (2007). Tracing syndrome-specific trajectories of attention across the lifespan. *Cortex*, 43, 672-685.

Cress, C. J., Aren, K., B. and Zajicek, A., K. (2007). Comparison of engagement patterns of young children with developmental disabilities between structured and free play. *Education and Training in Developmental Disabilities*, 42, 152 – 164.

Davidson, N. (1976). Causal inferences from dichotomous variables. *Concept and Technique in Modern Geography*, 9, 1-37.

De Lima Velloso, R. and Schwartzman, J.S. (2010). Concepts of color, shape, size and position in ten children with Rett syndrome. *Arquivos De Neuro-Psiquiatria*, 67, 50-54.

Dekker, M.C., Nunn, R. and Koot, H.M. (2002). Psychometric properties of the revised developmental behaviour checklist scale in Dutch children with Intellectual Disability. *Journal of Intellectual Disability Research*, 46, 61-75.

Didden, R., Korzilius, H., Smeets, E., Green, V.A., Lang, R., Lancioni, G. E. and 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.

Dosen, A. (2005). Applying the developmental perspective in the psychiatric assessment and diagnosis of persons with intellectual disability: Part I – Assessment. *Journal of Intellectual Disability Research*, 49, 1 – 8.

Dosen, A. (2005). Applying the developmental perspective in the psychiatric assessment and diagnosis of persons with intellectual disability: Part II –Diagnosis. *Journal of Intellectual Disability Research*, 49, 9 – 15.

Downs, J.A., Bebbington, A., Jacoby, P., Msall, M.E., Mcilroy, O., Fyfe, S., Bahi-Buisson, N., Kaufmann, W.E. and Leonard, H. (2008). Gross motor profile in Rett syndrome as determined by video analysis. *Neuropediatrics*, 39, 205-210.

Downs J., Bebbington A., Jacoby P., Williams A., Ghosh S., Kaufmann W.E. and Leonard H. (2010). The level of purposeful hand function is a marker for clinical severity in Rett syndrome. *Developmental Medicine and Child Neurology*, 52. 817-823.

Downs, J., Bebbington, A., Kaufmann, W.E. and Leonard, H. (2011). Longitudinal hand function in Rett syndrome. *Journal of Child Neurology*, 26, 334 – 340.

Dunn, E. (2001). Importance of Rett syndrome in child neurology. *Brain & Development*, 23, S38-S43

Dykens, E.M (1995). Measuring behavioral phenotypes: Provocations from the “New Genetics”. *American Journal on Mental Retardation*, 522-532.

Dykens E.M. (2001). Introduction to the special issue on behavioral phenotypes. *American Journal on Mental Retardation*, 106, 1-3.

Dykens, E.M., Hodapp, R. M. (2001). Research in mental retardation: toward an etiology approach. *Journal of Child Psychology and Psychiatry*, 42, 49-72.

Dykens, E.M. (2002). Are jigsaw puzzles ‘spared’ in persons with Prader-Willi syndrome? *Journal of Child Psychology and Psychiatry*, 43, 343-352.

Dykens E.M. (2003). Anxiety, fears, and phobias in persons with Williams syndrome, *Developmental Neuropsychology*, 23, 291-316.

Dykens, E.M. and Hodapp, R.M. (2007). Three steps toward improving the measurement of behavioural phenotype research. *Child and Adolescent Psychiatric Clinics of North America*, 16, 617-630.

Einfeld, S.L. and Tonge, B.J. (1994). *Manual for the Developmental Behaviour Checklist (Primary Career Version)*. Melbourne, Australia: Monash University Centre For Developmental Psychiatry.

Einfeld, S.L. and Tonge, B.J. (1995). The Developmental Behaviour Checklist: the developmental and validation of an instrument for the assessment of behavioural and emotional disturbance in children and adolescents with mental retardation. *Journal of Autism and Developmental Disorders*, 25, 81-104.

Einfield, S.L. (2004). Behaviour phenotypes of genetic disorders. *Current Opinion in Psychiatry*, 17, 343-348.

Einspieler, C., Kerr, A.M. and Precht H.F.R (2005). Is the early development of girls with Rett disorder really normal? *Paediatric Research*, 57, 696-700.

Eisenhower, A.S., Baker, B.L. and Blacher, J. (2009). Children’s delayed development and behavior problems: impact on mothers’ perceived physical health across early childhood. *Social Science & Medicine*, 68, 89 – 99.

Elefant, C. (2004). Rett syndrome: dual intervention- music and physical therapy. *Nordic Journal of Music Therapy*, 13(2), 172-182.

Elefant, C. and Wigram, T. (2005). Learning ability in children with Rett syndrome, *Brain & Development*, 27, S97-S101.

Elian, M. and Rudolf, N.D. (1989). Rett syndrome: some behavioural aspects and an overview. *Behavioural Neurology*, 2, 211-218.

Elian, M. and Rudolf, N.D. (1991). EEG and respiration in Rett syndrome. *Acta Neurologica Scandinavica*, 83, 123-128.

Elian, M. and Rudolf, N.D. (1996). Observations on hand movements in Rett syndrome: a pilot study. *Acta Neurologica Scandinavica*, 94, 212-4.

Ellaway, C., Peat, J., Leonard, H. and Christodoulou, J. (2001). Sleep dysfunction in Rett syndrome: lack of age related decrease in sleep duration. *Brain & Development*, 23, S101-S103.

Emerson, E., Hatton, C., Robertson, J., Henderson, D. and Cooper, J.A. (1999). descriptive analysis of the relationships between social context, engagement and stereotypy in residential services for people with severe and complex disabilities. *Journal of Applied Research in Intellectual Disabilities*, 12, 11 – 29.

Emerson E. (2003). Mothers of children and adolescents with intellectual disability: social and economic situation, mental health status, and the self-assessed social and psychological impact of the child's difficulties. *Journal of Intellectual Disability Research*, 47, 385 – 399.

Evans, I., M. and Meyer, L. H. (1999). Modifying adult interactional style as positive behavioural intervention for a child with Rett syndrome. *Journal of Intellectual and Developmental Disability*, 24, 191 – 205.

Fabio R.A, Martinazzoli, C. and Antonietti A., (2005). Costruzione e standardizzazione dello strumento "R.A.R.S." (Rett Assessment Rating Scale). *Ciclo Evolutivo e Disabilita' (Life Span And Disability)*, 8, 257-279.

Fabio, R. A., Giannatiempo, S., Antonietti, A. And Budden, S. (2009a). The role of stereotypies in overselectivity process in Rett syndrome. *Research In Developmental Disabilities*, 30, 136-145.

Fabio, R.A., Antonietti, A., Castelli, I. and Marchetti, A. (2009b). Attention and communication in Rett syndrome. *Research in Autism Spectrum Disorders*, 3, 329-335.

Fabio R.A and Giannatiempo S. (2009c). Discriminazione di differenti categorie semantiche: uso della tecnologia eye tracker nella sindrome di Rett. *Vivirett*, 54, 12-18.

Felce, D. (1996). The quality of support for ordinary living: Staff: Resident interactions and resident activity. In J. Mansell & K. Ericcson (Eds), *Deinstitutionalization and community living: Intellectual disability services in Britain, Scandinavia and the USA*. London: Chapman and Hall.

Felce, D., Bowley, C., Baxter, H., Jones, E., Lowe, K. and Emerson E. (2000). The effectiveness of staff support: Evaluating Active Support training using a conditional probability approach. *Research in Developmental Disabilities*, 21, 243 – 255.

Felce D. and Perry J. (2004). Resource input, service process and resident activity indicators in a Welsh national random sample of staffed housing services for people with intellectual disabilities. *Journal of Applied Research in Intellectual Disabilities*, 17, 127-132.

Field, A. (2009). *Discovering statistics using SPSS*, SAGE publications.

Finegan, J.A. (1998). Study of behavioural phenotypes: goals and methodological considerations. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, 81, 148-155.

Fitzgerald, P.M., Jankovic, J. and Percy, A.K. (1990). Rett syndrome and associated movement disorders. *Movement Disorders*, 5, 195-202.

Fontanesi, J. and Haas, R. (1988). Cognitive profile of Rett syndrome. *Journal of Child Neurology*, 3, S20-4.

Freiling, M., Bebbington, A., Lanator, I., De Klerk, N., Dunkler, D. Seidl, R.,

Leonard, H. and Ronen, G.M (2010). Survival with Rett syndrome: comparing Rett's original sample data from the Australian Rett syndrome database. *Developmental Medicine & Child Neurology*, 52, 962-965.

Friedrich, W.N., Greenberg, M.T. and Crnic, K. (1983). A short-form of the Questionnaire on Resources and Stress. *American Journal of Mental Retardation*, 88, 41- 48.

Gadalla, K.K.E., Bailey, M.E.S. and Cobb, S.R., (2011). Mecp2 and Rett syndrome: reversibility and potential avenue for therapy. *Biochemical Journal*, 439, 1-14.

Gardner, F. (2000). Methodological issues in the direct observation of parent-child interaction: do observational findings reflect the natural behavior of participants? *Clinical Child and Family Psychology Review*, 3, 185 – 197.

Gillberg, C. (1987). Autistic symptoms in Rett syndrome: the first two years according to mother reports. *Brain & Development*, 9, 499-501.

Gillberg, C. (1997). Communication in Rett syndrome complex. *European Child and Adolescent Psychiatry*, 6, 21-2.

Gillberg C. and Soderstrom, H. (2003). Learning disability. *The Lancet*, 362, 811-821.

Glaze, D.G., Frost J.D. Jr, Zoghbi H.Y. and Percy A.K. (1987). Rett syndrome: characterization of respiratory patterns and sleep. *Annal Neurology*, 21, 377-382.

Glaze, D.G., Schultz, R. and Frost, J. (1998). Rett syndrome: characterization of seizures versus non-seizures. *Electroencephalographic Clinical Neurophysiology*, 106, 79-83.

Glaze, D.G., (2004). Rett syndrome: of girls and mice-lessons for regression in autism. *Mental Retardation and Developmental Disabilities Research Review*, 10, 154-158

Glaze, D.G., Percy, A.K., Skinner, S., Motil, K.J., Neul, J.L., Barrish, J.O., Lane,

J.B., Geerts, S.P., Annese, F., Graham, J., McNair, L. and Lee, H.S. (2010). Epilepsy and the natural history of Rett syndrome. *Neurology*, 74, 909-12.

Goldman, S. and Temudo, T. (2012). Hand stereotypies distinguish Rett syndrome from autism disorder. *Movements Disorders*, 18, 1 – 4.

Goodey, C.F. (2006). Behavioural phenotypes in disability research: Historical perspectives. *Journal of Intellectual Disability Research*, 50, 397-403.

Goodman, R. (1997). The Strengths and Difficulties Questionnaire: A research note. *Journal of Child Psychology and Psychiatry*, 38, 581-586.

Goodman, R. (2001). Psychometric properties of The Strengths and Difficulties Questionnaire (SDQ). *Journal of The American Academy of Child and Adolescents Psychiatry*, 40, 1337-1345.

Greer, F., Grey, I.M. and Mcclean, B. (2006). Coping and positive perceptions in Irish mothers of children with intellectual disabilities. *Journal of Intellectual Disabilities*, 10, 231 – 248.

Griffith G.M., Hastings R.P., Nash S. and Hill C. (2010). Using matched groups to explore child behavior problems and maternal well-being in children with Down syndrome and Autism. *Journal of Autism and Developmental Disorders*, 40, 610 – 619.

Griffith G.M., Hastings R.P., Oliver C., Howlin P., Moss J., Petty J. and Tunnicliffe P. (2011). Psychological well-being in parents of children with Angelman, Cornelia de Lange and Cri du Chat syndromes, *Journal of Intellectual Disability Research*, 55, 397 – 410.

Guy, J., Hendrich, B., Holmes, M., Martin, J.E., and Bird A.A. (2001). Mouse *mecp2*-null mutation causes neurological symptoms that mimic Rett syndrome. *Nature Genetics*, 27, 322-326.

Guy, J., Gan, J., Selfridge, J., Cobb, S. and Bird, A. (2007). Reversal of neurological defects in a mouse model of Rett syndrome. *Science*, 315, 1143-1147.

Hagberg, B., Aicardi, J., Dias, K. and Ramos, O. (1983). A progressive syndrome of

autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett syndrome: report of 35 cases. *Annals of Neurology*, 14, 471-479.

Hagberg B. and Witt-Engestrom I. (1986). Rett syndrome: a suggested staging system for describing impairment profile with increasing age towards adolescence. *American Journal of Medical Genetics*, 24, 47-59.

Hagberg B. (2002). Clinical manifestations and stages of Rett syndrome. *Mental Retardation and Developmental Disabilities*, 8, 61-65.

Hagberg, B., Hanefeld, F., Percy, A. and Skjeldal, O. (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 Paediatric Neurology Society*, 6, 293-297.

Halbach N.S.J., Smeets E.E.J., Steinbusch C., Maaskant M.A., Van Waardenburg D., Curfs L.M.G. (2012). Aging in Rett syndrome: a longitudinal study. *Clinical Genetics*, 1 – 7.

Halbach, N.S., Smeets, E.E., Schrandt-Stumpel, C.T., Van Schrojenstein Lantman De Valk, H.H., Maaskant, M.A. and Curfs, L.M. (2008). Aging in people with specific genetic syndromes: Rett syndrome. *American Journal of Medical Genetics A*, 146a, 1925-32.

Hall S.S., Arron, K., Sloneem, J. and Oliver C. (2008). Health and sleep problems in Cornelia de Lange syndrome: a case control study. *Journal of Intellectual Disability Research*, 52, 458 – 468.

Hanks, S. (1986). The role of therapy in Rett syndrome. *American Journal of Medical Genetics Supplement* 1, 247-52.

Hanley, B., Tasse, M.J., Aman, M.G. and Pace, P. (1998). Psychometric properties of the Family Support Scale with Head Start families. *Journal of Child and Family Studies*, 7, 69 – 77.

Harris, J. (2010). Advances in understanding behavioral phenotypes in neurogenetic syndromes. *American Journal Of Medical Genetics Part C (Seminars In Medical Genetics)*, 154C, 389 – 399.

Hastings, R.P., Brown, T., Mount, R.H., And Cormack, M.K.F. (2001). Exploration of psychometric properties of The Developmental Behavior Checklist. *Journal of Autism And Developmental Disorders*, 31, 423-431.

Hastings, R.P. and Taunt, H.M. (2002a). Positive perceptions in families of children with developmental disabilities. *American Journal on Mental Retardation*, 107, 116 – 127.

Hastings R.P. (2002b). Parental stress and behaviour problems of children with developmental disability. *Journal of Intellectual and Developmental Disability*, 27, 149 – 160.

Hastings, R.P. (2003). Child behaviour problems and partner mental health as correlates of stress in mothers and fathers of children with autism. *Journal of Intellectual Disability Research*, 47, 231 – 237.

Hastings R.P. and Beck, A. (2004). Practitioner review: stress intervention for parents of children with intellectual disabilities. *Journal of Child Psychology and Psychiatry*, 45 1338 – 1349.

Hastings, R.P., Beck, A. and Hill, C. (2005). Positive contributions made by children with an intellectual disability in the family: mothers' and fathers' perceptions. *Journal of Intellectual Disabilities*, 9, 155 – 165.

Hatton D.D. Sideris J., Skinner M., Mankowski J., Bailey D.B. Jr, Roberts J. and Mirrett P. (2006). Autistic behavior in children with Fragile X syndrome: Relevance, stability, and the impact of FMRP. *American Journal of Medical Genetics* 140A, 1804–1813.

Hauser-Cram, P., Warfield, M.E., Shonkoff, J.P., Krauss, M.W., Upshur, C. and Sayer, A. (1999). Family influences on adaptive development in young children with

Down syndrome. *Child Development*, 70, 979 – 989.

Hayes, S., Mcguire B., O'Neill, M., Oliver, C. and Morrison, T. (2011). Low mood and challenging behaviour in people with severe and profound intellectual disabilities. *Journal of Intellectual Disability Research*, 55, 182 – 189.

Head, L. and Abbeduto, L. (2007). Recognizing the role of parents in developmental outcomes: a systems approach to evaluating the child with developmental disabilities. *Mental Retardation and Developmental Disabilities*, 13, 293 – 301.

Hendrick, D., Prather, E., Tobin, A. (1975). *Sequenced Inventory of Communication Development*. Seattle: University Of Washington Press.

Hetzroni, O. and Konkol, O. (2002). The use of assistive technology for symbol identification by children with Rett syndrome. *Journal of Intellectual and Developmental Disability*, 27, 57-71.

Hetzroni, O. and Rubin, C. (2006). Identifying patterns of communicative behaviors in girls with Rett syndrome. *Augmentative & Alternative Communication*, 22, 48-61.

Hill, S. (1997). The relevance and value of music therapy for children with Rett syndrome. *British Journal Of Special Education*, 24, 124-128.

Hite, K.C., Adams, V.H. and Hansen, J.C. (2009). Recent advances in MeCP2 structure and function. *Biochemical Cell Biology*, 87, 219-227.

Hodapp, R.M. (1997). Direct and indirect behavioural effects of different genetic disorders of mental retardation. *American Journal on Mental Retardation*, 102, 67-79.

Hodapp, R.M. (1999). Syndromes, phenotypes and genotypes. Finding the links. *The Psychologist*, 12, 242-245.

Hodapp, R.M. and Dykens E.M. (2001). Strengthening behavioural research on genetic mental retardation syndromes. *American Journal on Mental Retardation*, 106, 4-15.

Hodapp, R.M. (2004a). Studying interactions, reactions and perceptions: Can genetic

disorders serve as behavioural proxies? *Journal of Autism and Developmental Disorders*, 34, 29-34.

Hodapp, R.M. (2004b). Behavioural phenotypes: Going beyond the two-group approach. *International Review of Research in Mental Retardation*, 49, 1-29.

Holland, A.J., Whittington, J.E., Butler, J., Webb, T., Boer, H. and Clarke, D. (2003). Behavioural phenotypes associated with specific genetic disorders: evidence from a population-based study of people with Prader-Willi syndrome. *Psychological Medicine*, 33, 141-153.

Honey, E., Hastings, R.P. and McConachie, H. (2005). Use of the questionnaire on resources and stress (QRS-F) with parents of young children with autism. *Autism*, 9, 243-252.

Horsler, K. and Oliver, C. (2006a). The behavioural phenotype of Angelman syndrome. *Journal of Intellectual Disability Research*, 50, 33 – 53.

Horsler, K. and Oliver, C. (2006b). Environmental influences on the behavioural phenotype of Angelman syndrome. *American Journal on Mental Retardation*, 111, 311-321.

Hu, X., Summers, J.A. and Zuna, N. (2011). The quantitative measurement of family quality of life: A review of available instruments. *Journal of Intellectual Disability Research*, 55, 1098 – 1114.

Huppke P., Held M., Laccone F. and Hanefeld F. (2003). The spectrum of phenotypes in females with Rett syndrome. *Brain & Development*, 25, 346-351

Huppke, P. Maier E.M., Warnke, A., Brendel, C., Laccone, F., Gartner, J. (2006). Very mild cases with Rett syndrome with skewed X inactivation. *Journal of Medical Genetics*, 43, 814 – 816.

Hwa Ha, J., Hong, J., Seltzer, M.M. and Greenberg, J.S. (2008). Age and gender differences in the well-being of midlife and aging parents with children with mental health or developmental problems: report of a national study. *Journal of Health and*

*Social Behavior*, 49, 301 – 316.

Hyman, P., Oliver, C. and Hall, S. (2002). Self-injurious behaviour, self restraint and compulsive behaviour in Cornelia de Lange syndrome. *American Journal on Mental Retardation*, 107, 146-154.

Iwata B.A., Pace, G.M., Willis, K.D., Gramache, T.B., Hyman, S.L. (1986). Operant studies of self-injurious hand biting in the Rett syndrome. *American Journal of Medicine*, Suppl, 1, 157-166.

Jones, J. and Passey, J. (2004). Family adaptation, coping and resources: Parents of children with developmental disabilities and behaviour problems. *Journal on Developmental Disabilities*, 11, 31 – 46.

Julu, P., Kerr, A., Apartopoulos, F., Al-Rawas, S., Witt-Engerstrom, I., Engerstrom, L., Jamal, G. and Hansen, S. (2001). Characterisation of breathing and associated central autonomic dysfunction in the Rett disorder. *Archives of Disease in Childhood*, 85, 29-37.

Kaufmann, W.E., Tierney, E., Rohde, C.A., Suarez-Pedraza, M.C., Clarke, M.A., Salorio, C.F., Bibat, G., Bukelis, I., Naram, D., Lanham, D.C., Naidu, S. (2011). Social impairments in Rett syndrome: Characteristics and relationship with clinical severity. *Journal of Intellectual Disability Research*, 56, 233–247,

Kerr A. M. and Ravine D. (2003). Review article: breaking new ground with Rett syndrome. *Journal of Intellectual Disability Research*, 47, 580-587.

Kerr, A.M., Archer, H.L., Evans, J.C., Prescott, R.J. and Gibbon, F. (2006). People with *MECP2* mutation-positive Rett disorder who converse. *Journal of Intellectual Disability Research*, 50 386-394.

Kerr, A.M., Montague J. and Stephenson J.B.P (1987). The hands, and the mind, pre- and post regression in Rett syndrome. *Brain & Development*, 9, 487-490.

Kerr, A., Southall, D., Amos, P., Cooper, R., Samuels, M., Mitchell, J. and Stephenson, J. (1990). Correlation of electroencephalogram, respiration and movement

in the Rett syndrome. *Brain & Development*, 12, 61-8.

Kerr, A.M. and Witt-Engerstrom, I. (2001). The developmental perspective in the Rett disorder: where next? In A.M. Kerr and I. Witt-Engerstrom (Eds), *Rett Disorder and The Developing Brain*, Oxford University Press, Oxford.

Kline, A.D., Grados, M., Sponseller, P., Levy, H.P., Blagowidow, N., Schoedel, C., Rampolla, J., Clemens, D.K., Krantz, I., Kimball, A., Pichard, C. and Tuchman, D. (2007). Natural history of aging in Cornelia de Lange syndrome. *American Journal of Medical Genetics Part C (Seminars In Medical Genetics)*, 145C, 248 – 260.

Kondo M., Gray L.J., Pelka G.J., Christoulou J., Tam P.P. and Hannan A.J. (2007). Environmental enrichment ameliorates a motor coordination deficit in a mouse model of Rett syndrome. Mecp2 gene effects and BDNF expression. *European Journal of Neuroscience*, 27, 3342-3350.

Koppenhaver, D.A., Erickson, K.A., Harris, B., Mcllellan, J., Skotko, B.G. and Newton, R.A. (2001). Storybook-based communication intervention for girls with Rett syndrome and their mothers. *Disability and Rehabilitation: An International, Multidisciplinary Journal*, 23, 149-159.

Kubas E. (1992). Use of splints to develop hand skills in a woman with Rett syndrome. *The American Journal of Occupational Therapy*, 46, 364 – 368.

Larsson, G. and Witt-Engerstrom, I. (2001). Gross motor ability in Rett syndrome - The power of expectation, motivation and planning. *Brain & Development*, 23, S77-S81.

Laurvick, C.L., Msall, M.E., Silburn, S., Bower, C., De Klerk, N. and Leonard, H. (2006). Physical and mental health of mothers caring for a child with Rett syndrome. *Pediatrics*, 118, E1152 – E1164.

Lavas, J., Slotte, A., Jochym-Nygren, M., Van Doorn, J. and Witt-Engerstrom, I. (2006). Communication and eating proficiency in 125 females with Rett syndrome: The Swedish Rett Center Survey. *Disability and Rehabilitation*, 28, 1267-1279.

Lecavalier, L., Leone, L. and Wiltz, J. (2006) The impact of behaviour problems on caregiver stress in young people with autism spectrum disorders. *Journal of Intellectual Disability Research*, 50, 173 - 183

Leonard H., Covin, L., Christodoulou, J., Schiavello, T., Williamson, S., Davis, M., Ravine, D., Fyfe, S., De Klerk, N., Matsuishi, T., Kondo, I., Clarke, A., Hackwell, S. and Yamashita, Y. (2003). Patients with R133C mutation: Is their phenotype different from patients with Rett syndrome with other mutations? *Journal of Medical Genetics*, 40, 1-7.

Leonard, H. and Bower, C. (1998). Is the Rett syndrome normal at birth? *Developmental Medicine and Child Neurology*, 40, 115-121.

Leonard, H., Fyfe, S., Leonard, S. and Msall, M. (2001). Functional status, medical impairments, and rehabilitation resources in 84 females with Rett syndrome: a snapshot across the world from the parental perspective. *Disability & Rehabilitation*, 23, 107-17.

Leonard, H., Moore M., Carey M., Fyfe S., Hall S., Robertson L., Xi Ru Wu, Bao X., Pan H., Christodoulou J., Williamson S. and De Klerk N. (2005). Genotype and early development in Rett syndrome: The value of international data. *Brain & Development*, 27, S59-S68.

Lloyd, T and Hastings, R.P (2008). Psychological variables as correlates of adjustment in mothers of children with intellectual disabilities: cross-sectional and longitudinal relationship. *Journal of Intellectual Disability Research*, 52, 37 – 48.

Luzzani, S., Macchine, F., Valade, A., Milani, D. and Selicorni, A. (2003). Gastroesophageal reflux and Cornelia de Lange syndrome: Typical and atypical symptoms. *American Journal of Medical Genetics*, 119A, 283-287.

Macdonald, E.E., Hastings, R.P. and Fitzsimons, E. (2010). Psychological acceptance mediates the impact of the behaviour problems of children with intellectual disability on fathers' psychological adjustment. *Journal of Applied Research in Intellectual Disabilities*, 23, 27-37.

Mansell, J., Elliott, T., Beadle-Brown, J., Ashman, B. and Macdonald, S. (2002).

Engagement in meaningful activities and “active support” of people with intellectual disabilities in residential care. *Research in Developmental Disabilities*, 23, 342 – 352.

Marcus, C.L., Carroll, J.L., Mccolley, S.A., Loughlin, G.M., Curtis, S., Pyzik, P. and Naidu, S. (1994). Polysomnographic characteristics of patients with Rett-syndrome. *Journal of Pediatrics*, 125, 218-224.

Martin, N., Oliver, C. and Hall, S. (2001). *Obswin: Software for the Collection and Analysis of Observational Data*. University Of Birmingham, Birmingham UK.

Masuyama T., Matsuo M., Jing J.J., Tabara Y., Kitsuki K., Yamagata H., Kan Y., Miki T., Ishii K. and Kondo I. (2005). Classic Rett syndrome in a boy with R133C mutation of *MECP2*. *Brain & Development*, 27, 439-442.

Matson J.L, Carlisle, C.B., Bamburg, J.W. (1998). The convergent validity of The Matson Evaluation of Social Skills in Persons With Severe Retardation (MESSIER). *Research in Developmental Disabilities*, 19, 493-500.

Matson, J.L., Dempsey, T. and Wilkins, J. (2008). Rett syndrome in adults with severe intellectual disability: Exploration of behavioral characteristics. *European Psychiatry*, 23, 460-465.

Mazzocco, M.M.M., Pulsifer, M., Fiumara, A., Cocuzza, M., Nigro, F., Incorpora, G. and Barone, R. (1998). Brief report: autistic behaviors among children with Fragile X or Rett syndrome: implications for the classification of Pervasive Developmental Disorder. *Journal of Autism and Developmental Disorders*, 28, 321-328.

McArthur, A. J. and Budden, S.S. (1998). Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. *Developmental Medicine and Child Neurology*, 40, 186-192.

Mervis, C. and Klein-Tasman, B.P. (2004). Methodological Issues in Group-Matching Designs:  $\alpha$  Levels for Control Variable Comparisons and Measurement Characteristics of Control and Target Variables. *Journal of Autism and Developmental Disorders*, 34, 7 – 17

Meloni, I., Bruttini, M., Longo, I., Mari, F., Rizzolio, F., D'Adamo, P., Denvriend, K., Fryns, J., Toniolo, D. and Renieri, A. (2000). A mutation in the Rett syndrome gene, *MECP2*, causes X-linked mental retardation and progressive spasticity in males. *American Journal of Human Genetics*, 67, 982-985.

Mohr, C., Tonge, B. and Einfeld, S.L. (2005). The development of a new measure for the assessment of psychopathology in adults with intellectual disability. *Journal of Intellectual Disability Research*, 49, 469-480.

Mohr, C., Tonge, B., Taffe, J., Rymill, A., Collins, D., Keating, C. and Einfeld, S.L. (2011). Inter-rater reliability of the developmental behaviour checklist for adult in community accommodation settings. *Journal of Intellectual Disability Research*, 55, 710-713.

Morton, R., Bonas, R., Minford, J., Tarrant, S. and Ellis, R. (1997). Respiration patterns during feeding in Rett syndrome. *Developmental Medicine and Child Neurology*, 39, 607-13.

Morton, R., Pinnington, L. and Ellis, R. (2000). Air swallowing in Rett syndrome. *Developmental Medicine and Child Neurology*, 42, 271-5.

Moss, J., Oliver, C., Hall, S., Arron, K., Sloneem, J and Petty, J. (2005). The association between environmental events and self-injurious behaviour in Cornelia de Lange syndrome. *Journal Of Intellectual Disability Research*, 49, 269 – 277.

Moss, J., Oliver, C., Arron, K., Burbidge, C. and Berg, K. (2009). The prevalence and phenomenology of repetitive behaviour in genetic syndromes, *Journal of Autism and Developmental Disorder*, 39, 572 – 588.

Motil, K.J., Schultz, R.J., Browning, K., Trautwein, L., Glaze, D.G. (1999). Oropharyngeal dysfunction and gastroesophageal dysmotility are present in girls and women with Rett syndrome. *Journal of Pediatric Gastroenterology & Nutrition*, 29, 31 – 37

Mount, R.H., Hastings, R.P., Reilly, S., Cass, H. and Charman, T. (2001)

Behavioural and emotional features in Rett syndrome. *Disability and Rehabilitation*, 23, 129 – 138.

Mount, R.H., Charman, T., Hastings, R., Reilly, S. and Cass, H. (2002a). The Rett Syndrome Behaviour Questionnaire (RSBQ): refining the behavioural phenotype of Rett syndrome. *Journal of Child Psychological Psychiatry*, 43, 1099-1110.

Mount, R.H., Hastings, R.P., Reilly, S., Cass, H. and Charman, T. (2002b). Behaviour problems in adult women with Rett syndrome. *Journal Of Intellectual Disability Research*, 46, 619 – 624.

Mount R.H., Charman T., Hastings R.P, Reilly S. and Cass H. (2003a). Features of autism in Rett syndrome and severe mental retardation. *Journal of Autism and Developmental Disorders*, 33, 435-442.

Mount, R.H., Hastings, R.P., Reilly, S., Cass, H. and Charman, T. (2003b). Towards a behavioral phenotype for Rett syndrome. *American Journal on Mental Retardation*, 108, 1-12.

Mulroy, S., Robertson, L., Aiberti, K., Leonard, H. and Bower, C. (2008). The impact of having a sibling with an intellectual disability: Parental perspectives in two disorders. *Journal of Intellectual Disability Research*, 52, 216 – 229.

Mykletun A., Stordale E. and Dahal A. A. (2001). Hospital Anxiety and Depression (HAD) Scale: Factor structure, item analyses and internal consistency in a large population. *British Journal of Psychiatry*, 179, 540-544.

Naganuma G. and Billingsley F. (1988). Effect of hand splints on stereotypic hand behaviours of three girls with Rett syndrome. *Physical Therapy*, 68, 664-671

Neul, J.L., Fang, P., Barrish, J., Lane, J., Caeg, E. B., Smith, E.O., Zoghbi, H., Percy, A. and Glaze, D.G. (2008). Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. *Neurology*, 70, 1313-21.

Neul, J.L, Kaufmann, W, Glaze, D.G., Christodoulou, J., Clarke, A.J., Bahi-Buisson, N., Leonard, H., Bailey, M.E.S., Schanen, C.N., Zappella, M., Ranieri, A., Huppke, P.

and Percy, A.K. (2010). Rett syndrome: revised diagnostic criteria and nomenclature. *Annals of Neurology*, 68, 944-950.

Nomura Y. and Segawa M., (2005). Natural history of Rett syndrome. *Journal of Child Neurology*, 20, 764-768.

Nomura, Y., Kimura, K., Arsi, H. and Segawa, M. (1997). Involvement of the autonomic nervous system in the pathophysiology of Rett syndrome. *European Child and Adolescent Psychiatry*, 6, 42-46.

Nyhan, W. (1972). Behavioural phenotypes of organic genetic disease. Presidential Address to The Society of Pediatric Research, May 1, 1971. *Pediatric Research*, 6, 1-9.

O'Brien, G. (2000). Behavioural phenotypes. *Journal of The Royal Society of Medicine*, 93, 618-620.

O'Brien, G. (2002). *Behavioural Phenotypes In Clinical Practice*. London: Mac Keith; Cambridge.

O'Brien, G. (2006). Behavioural phenotypes: Causes and clinical implications. *Advances in Psychiatry Treatment*, 12, 338-348.

Oliver, C., Murphy, G.H., Crayton, L. and Corbett, J.A. (1993). Self-injurious behavior in Rett syndrome: Interactions between features of Rett syndrome and operant conditioning. *Journal of Autism and Developmental Disorders*, 23, 91-109.

Oliver, C., Horsler, K., Berg, K., Bellamy, G., Dick, K. and Griffiths, E. (2007a). Genomic imprinting and the expression of affect in Angelman syndrome: what's in the smile. *Journal of Child Psychology and Psychiatry*, 48, S71-S79.

Oliver, C. and Hagerman (2007b). Trends and challenges in behavioural phenotypes research. *Journal of Intellectual Disability Research*, 51, 649-652

Oliver, C. and Woodcock, K. (2008). Integrating levels of explanation in behavioural phenotype research. *Journal of Intellectual Disability Research*, 52, 807-809.

Oliver, C., Sloneem, J. and Arron, K. (2009). Self-injurious behaviour in Cornelia de

Lange syndrome: I. Prevalence and phenomenology. *Journal of Intellectual Disability Research*, 53, 575-589.

Oliver, C., Woodcock, K. and Adams, D. (2010). The importance of aetiology of intellectual disability, In: Grant, G., Ramcharan, P., Flynn, M., and Richardson, M. (Eds), *Learning Disability: A Life Cycle Approach To Valuing People*, 2<sup>nd</sup> Edition. Publisher By Open University, McGraw Hill, 135-146.

Oliver C., Berg, K., Moss, J., Arron, K., Burbidge, C. (2011). Delineation of behavioural phenotypes in genetic syndromes: Characteristics of Autism Spectrum Disorder, affect and hyperactivity. *Journal of Autism and Developmental Disorders*, 41, 1019-1032.

Oliver, C., Petty, J., Ruddick, L. and Bacarese-Hamilton, M. (2012). The association between repetitive, self-injurious and aggressive behavior in children with severe intellectual disability. *Journal of Autism and Developmental Disorders*, 42, 910 – 919.

Oliver, C., Arron, K., Burbidge, C, Mace, H., Moss, J., Ross, E. and Russell, H. (In Review), *Manual For The: Repetitive Behaviour Questionnaire (RBQ), Activity Questionnaire (TAQ), Mood Interest And Pleasure Questionnaire (MIPQ), Food Related Problem Questionnaire (FRPQ)*. Cerebra Centre for Neurodevelopmental Disorders, School Of Psychology, University Of Birmingham.

Olsson, B. (1987). Autistic Traits In The Rett Syndrome. *Brain And Development*, 9, 491-8.

Olsson, B. and Rett, A. (1985). Behavioral observations concerning differential diagnosis between the Rett syndrome and autism. *Brain & Development*, 7, 281-9.

Olsson, B. and Rett, A. (1987). Autism and Rett syndrome: Behavioural investigations and differential diagnosis. *Developmental Medicine and Child Neurology*, 29, 429-441.

Opitz, J.M. and Lewin, S.O. (1987). Rett syndrome - a review and discussion of syndrome delineation and syndrome definition. *Brain and Development*, 9, 445-450.

Ott, R.L., Larson, R., Rexroat, C. and Mendenhall, W. (1992). *Statistics: A tool for the social science*. New York (5<sup>th</sup> ed.). Boston: PWS-Kent Publishing Company.

Paterson, S.J. (2010). A developmental approach to genetic disorders. In: M. A. Barnes (Eds), *Genes, Brain And Development. The Neurocognition of Genetic Disorders*, Cambridge University Press, 175-198.

Pedersen, S.D., Parson, H.G. and Dewey, D. (2004). Stress levels experienced by the parents of entirely fed children. *Child: Care, Health and Development*, 30, 507 – 513.

Percy, A., Zoghbi, H., Lewis, K. and Jankovic, J. (1988). Rett syndrome: qualitative and quantitative differentiation from autism. *Journal of Child Neurology*, 3, S65-S67

Percy, A.K. (2001). Rett syndrome: Clinical correlates of the newly discovered gene. *Brain and Development*, 23, S202 - S205

Percy A.K. (2008). Rett syndrome: Recent research progress. *Journal of Child Neurology*, 23, 543-9

Percy A.K., Neul, J.L., Glaze, D.G., Motil, K.J., Skinner, S.A., Khwaja, O., Lee, H. S., Lane, J.B., Barrish, J.O., Annese, F., Mcnair, L., Graham, J. and Barnes, K. (2010). Rett syndrome diagnostic criteria: Lessons from the natural history study. *Annals Of Neurology*, 68, 951-955

Percy, A.K. (2011). Rett Syndrome. Exploring The Autism Link. *Archives Of Neurology*, 68, 985-989

Perry, A., Sarlo-Mcgarvey, N. and Haddad, C. (1991). Brief report: Cognitive and adaptive functioning in 28 girls with Rett syndrome. *Journal of Autism Developmental Disorders*, 21, 551-6.

Perry A., Sarlo-Mcgarvey N. and Factor D.C. (1992). Stress and family functioning in parents of girls with Rett syndrome. *Journal of Autism and Developmental Disorders*, 22, 235 – 248

Perry, A. (2004). A model of stress in families of children with developmental disabilities: Clinical and research applications. *Journal on Developmental Disabilities*,

Petry, K., Kuppens, S., Vos, P. and Maes, B (2010). Psychometric evaluation of the Dutch version of the Mood, Interest and Pleasure Questionnaire (MIPQ). *Research in Developmental Disabilities*, 31, 1652 – 1658

Petty, J. and Oliver, C. (2005). Self – injurious behaviour in people with intellectual disability. *Current Opinion in Psychiatry*, 18, 484 – 489

Piazza, C., Fisher, W., Kieseewetter, K., Bowman, L. and Moser, H. (1990). Aberrant sleep patterns in children with the Rett syndrome. *Brain and Development*, 12, 488-93.

Piazza, C.C., Anderson, C. and Fisher, W. (1993). Teaching self-feeding skills to patients with Rett syndrome. *Developmental Medicine and Child Neurology*, 35, 991-996.

Pintaudi, M., Calevo, M.G., Vignoli, A., Parodi, E., Aiello, F., Baglietto, M.G., Hayek, Y., Buoni, S., Renieri, A., Russo, S., Cogliati, F., Giordano, L., Canevini, M. and Veneselli, E. (2010). Epilepsy in Rett syndrome: Clinical and genetic features. *Epilepsy and Behavior*, 19, 296 – 300.

Pit-Ten Cate, I. (2003). *Positive gain in mothers of children with physical disabilities*. Unpublished Doctoral Dissertation, University Of Southampton, UK.

Raina, P., O'Donnell, M., Rosenbaum, P., Brehaunt, J., Walter, S.D., Russell, D., Swinton, M., Zhu, B. and Wood, E. (2004). The health and well-being of caregivers of children with cerebral palsy. *Pediatrics*, 115, E626 – E636.

Roane, H., Piazza, C., Sgro, G., Volkert, V. and Anderson, C. (2001). Analysis of aberrant behaviour associated with Rett syndrome. *Disability and Rehabilitation*, 23, 139-48.

Robertson, L., Hall, S., Jacoby, P., Ellaway, C., De Klerk, N. and Leonard, H. (2006). The association between behavior and genotype in Rett syndrome using The Australian Rett Syndrome Database. *Neuropsychiatric Genetic*, 141b, 177-83.

Rohdin, M., Fernell, E., Eriksson, M., AlbaGe, M., Lagercrantz, H. and Katz-

Salamon, M. (2007). Disturbances in cardiorespiratory function during day and night in Rett syndrome. *Pediatric Neurology*, 37, 338-44.

Roof E., Stone W., Maclean W., Feurer I.D., Thompson T. and Butler M.G. (2000). Intellectual characteristics of Prader-Will syndrome: comparison of genetic subtypes. *Journal of Intellectual Disability Research*, 44, 25-30.

Ross, E. and Oliver, C. (2002). The relationship between levels of mood, interest and pleasure and 'challenging behaviour' in adults with severe and profound intellectual disability. *Journal of Intellectual Disability Research*, 46, 191 – 197.

Ross, E. and Oliver, C. (2003a). The assessment of mood in adults who have severe or profound mental retardation. *Clinical Psychology Review*, 23, 225- - 245.

Ross, E. and Oliver, C. (2003b). Preliminary analysis of the psychometric properties of the Mood, Interest And Pleasure Questionnaire (MIPQ) for adults with severe and profound learning disabilities. *British Journal of Clinical Psychology*, 42, 81 – 93.

Ryan, D., McGregor, F., Akermanis, M., Southwell, K., Ramke, M. and Woodyatt, G. (2004). Facilitating communication in children with multiple disabilities: Three case studies of girls with Rett syndrome. *Disability and Rehabilitation*, 26, 1268-77.

Sackett, G. (1978). *Observing behaviour: Data collection and analysis methods*, NICHD Mental Retardation Research Centers Series, University Park Press.

Saloviita, T. Italinna, M. and Leinonen, E. (2003). Explaining the parental stress of fathers and mothers caring for a child with intellectual disability: A double ABCX Model. *Journal of Intellectual Disability Research*, 47, 300 – 312.

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

Sansom, D., Krishnan, V., Corbett, J. and Kerr, A. (1993). Emotional and behavioural aspects of Rett syndrome. *Developmental Medicine and Child Neurology*, 35, 340-5.

Schanen, N.C., Kuczynski, T.W., Brunelle, D., Woodcock, L.S., Dure, L.S. and Percy, A.K. (1998). Neonatal encephalopathy in two boys in families with recurrent Rett syndrome. *Journal of Child Neurology*, 13, 229-231

Schieve L.A., Blumberg S.J., Rice C., Visser S.N. and Boyle S. (2007). The relationship between autism and parenting stress. *Pediatrics*, 119, S114 – S121.

Schwartzman, J. S., Zatz, M., Dos Reis Vasquez, L., Ribeiro Gomes R., Koiffmann, C. P., Fridman, C. and Guimaraes Otto P. (1999). Rett syndrome in a boy with a 47, XXY karyotype. *American Journal of Human Genetics*, 64, 1781-1785.

Segawa M. (2005). Early motor disturbances in Rett syndrome and its pathophysiological importance. *Brain & Development*, 27, S54-S58.

Segawa, M. and Nomura, Y. (1992). Polysomnography in the Rett syndrome. *Brain & Development*, 14, S46-S54.

Seltzer, M.M. and Heller, T. (1997). Introduction: Families and caregiving across the life course: Research advances on the influence of context. *Family Relations*, 46, 321 – 323.

Seltzer, M.M., Abbeduto, L., Wyngaager Krauss, M., Greenberg, J and Swe, A (2004). Comparison groups in Autism family research: Down syndrome, Fragile X syndrome and Schizophrenia. *Journal of Autism and Developmental Disabilities*, 43, 41 – 48 .

Sharpe, P.A. (1992). Comparative effects of bilateral hand splints and an elbow orthosis on stereotypic hand movements and toy play in two children with Rett syndrome. *American Journal of Occupational Therapy*, 46, 134-140.

Sharpe, P.A. and Ottenbacher, K.J. (1990). Use of an elbow restraint to improve finger-feeding skills in a child with Rett syndrome. *American Journal of Occupational Therapy*, 44, 328-332.

Sheskin, D.J. (2003). *Handbook Of Parametric and Nonparametric Statistic Procedures*, (Third Edition), Chapman And Hall.

Shoumitro, D., Dhaliwal, A. and Meera, R. (2009). The usefulness of the DBC-ASA as a screening instrument for autism in children with intellectual disabilities: A pilot study. *Journal of Applied Research in Intellectual Disabilities*, 22, 498-501.

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

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

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

Sigafoos, J., Arthur-Kelly, M. and Butterfield, N. (2006). *Enhancing Everyday Communication for Children with Disabilities*, Paul Brookes Publishing, Baltimore.

Singh J., Saxena A., Christodoulou J. and Ravine D. (2008). *MECP2* genomic structure and function: Insights from ENCODE. *Nucleic Acids Research*, 36, 6035 – 6047.

Siriani N., Naidu S., Pereira J. and Hoffman, E.P. (1998). Rett syndrome: Confirmation of X-linked dominant inheritance, and localization of the gene to Xq28. *American Journal of Human Genetics*, 63, 1552 – 1558.

Skotko, B.G. and Erickson, K.A. (2004). Parent reading behaviors and communication outcomes in girls with Rett syndrome. *Exceptional Children*, 70, 145-166.

Skuse, S. (2008). Behavioural phenotypes. *Psychiatry*, 7, 308-313.

Skuse, D.H., Seigal, A. (2008). Behavioral phenotypes and chromosomal disorders. In: M., Rutter, D., Bishop, D., Pine, S., Scott, J., Stevenson, E., Taylor and Thapar A. (Eds), *Child And Adolescent Psychiatry*, 5<sup>th</sup> Edition, Blackwell Publishing, 359-373.

Sleizter M.M., Abbeduto, L., Krauss, M.W., Greenberg, J. and Swe, A. (2004). Comparison groups in autism family research: Down syndrome, Fragile X syndrome and schizophrenia. *Journal of Autism and Developmental Disorders*, 34, 41-48.

Smeets E.E.J., Chenault M., Curfs L.M.G., Schrandt-Stumpel C.T.R.M., and Frijns J.P. (2009). Rett syndrome and long-term disorder profile. *American Journal of Medical Genetics Part A*, 149A, 199-205.

Smith, T., Klevstrand, M. and Lovaas, O.I. (1995). Behavioral treatment of Rett's disorder: Ineffectiveness in three cases. *American Journal on Mental Retardation*, 100, 317-322.

Southall, D., Kerr, A., Tirosh, E., Amos, P., Lang, M. and Stephenson, J. (1988). Hyperventilation in the awake state: Potentially treatable component of Rett syndrome. *Archives of Disease in Childhood*, 63, 1039-48.

Sparrow, S.S., Balla, D. and Cicchetti, D.V. (1984). *Vineland Adaptive Behavior Scales (Survey Ed.)*. Circle Pines, MN: American Guidance Service.

Stromme, P. and Hagberg, B. (2000). Aetiology in severe and mild retardation: a population-based study of Norwegian children. *Developmental Medicine and Child Neurology*, 42, 76-86.

Tams-Little, S. and Holdgrafer, G. (1996). Early communication development in children with Rett syndrome. *Brain & Development*, 18, 376-8.

Tao, J., Hu, K., Chang, Q., Wu, H., Sherman, N.E., Martinowich, K., Klose, R.J., Schanen, C., Jaenisch, R., Wang, W. and Sun, Y. E. (2009). Phosphorylation of MeCP2 at serine 80 regulates its chromatin association and neurological function. *Proceeding of The National Academy of Sciences*, 106, 4882-4887.

Taylor, M.J., Crowley, S.L. and White, K.R. (1993). Measuring family support and resources: psychometric investigation of the FSS and FRS. Paper presented at the Annual Meeting of the National Council on Measurement in Education, Atlanta, GA, April 13 – 15, 1993.

Taylor, L. and Oliver, C. (2008). The behavioural phenotype of Smith-Magenis syndrome: Evidence for a gene-environment interaction. *Journal of Intellectual Disability Research*, 52, 830 – 841.

Temudo, T., Oliveira, P., Santos, M., Dias, K., Vieira, J., Moreira, A., Calado, E., Carrilho, I., Oliveira, G., Levy, A., Barbot, C., Fonseca, M., Cabral, A., Dias, A., Cabral, P., Monteiro, J., Borges, L., Gomes, R., Barbosa, C., Mira, G., Eusbio, F., Sequeiros, J. and Maciel, P. (2007). Stereotypies in Rett syndrome: analysis of 83 patients with and without detected *MECP2* mutations. *Neurology*, 68, 1183-7.

Temudo, T., Ramos, E., Dias, K., Barbot, C., Vieira, J., Moreira, A., Calado, E., Carrilho, I., Oliveira, G., Levy, A., Fonseca, M., Cabral, A., Cabral, P., Monteiro, J., Borges, L., Gomes, R., Santos, M., Sequeiros, J. and Maciel, P. (2008). Movement disorders in Rett syndrome: An analysis of 60 patients with detected *MECP2* mutation and correlation with mutation type. *Movement Disorders*, 23, 1384-90.

Temudo T., Maciel P. and Sequeiros J. (2007). Abnormal movements in Rett syndrome are present before the regression period: a case study. *Movements Disorders*, 22, 2284-2287.

Thapar, A. and Rutter, M. (2008). Genetics. In: M., Rutter, D., Bishop, D., Pine, S., Scott, J., Stevenson, E., Taylor and A., Thapar (Eds). *Child and Adolescent Psychiatry*, 5<sup>th</sup> Edition, Blackwell Publishing, 339-358.

Wing L., Leekam S.R., Libby S.J., Gould J. and Larcombe M. (2002). The Diagnostic Interview for Social and Communication Disorders: Background, inter-rater Reliability and clinical use. *Journal of Clinical Psychology and Psychiatry*, 43, 307-325.

The Rett Syndrome Diagnostic Criteria Work Group. Diagnostic Criteria for Rett Syndrome. The Rett Syndrome Diagnostic Criteria Work Group (1988). *Annals Neurology*, 23, 425 – 428.

Thompson, T., Felce, D. and Symons F. J. (2000). *Behavioural Observation. Technology and Application in Developmental Disabilities*, Paul H Brooks Publishing Co, London.

Tonge, B. and Einfeld, S. (2000). The trajectory of psychiatric disorders in young people with intellectual disabilities. *Australian and New Zealand Journal of Psychiatry*, 34, 80-84.

Trevarthen, C. and Daniel, S. (2005). Disorganized rhythm and synchrony: early signs of autism and Rett syndrome. *Brain & Development*, 27 Suppl 1, S25-S34.

Tuten H. and Miednaer J. (1989). Effect of hand splints on stereotypic behaviour of girls with Rett syndrome: A replication study. *Physical Therapy*, 69, 1099 – 1103.

Uchino, J., Hoshino, K. and Segawa, M. (2001). Development of language in Rett syndrome. *Brain & Development*, 23, S233-S235.

Umansky, R. and Watson, J. (1998). Influence of eye movements on Rett stereotypies: Evidence suggesting a stage-specific regression. *Journal of Child Neurology*, 13, 158-62.

Umansky, R., Watson, J., Colvin, L., Fyfe, S., Leonard, S., De Klerk, N. and Leonard, H. (2003). Hand preference, extent of laterality, and functional hand use in Rett syndrome. *Journal of Child Neurology*, 18, 481-7.

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

Van Acker, R. (2010). Rett syndrome: A pediatric neurodevelopmental disorder, in F. Volkmar (Eds.), *Autism and Autism Spectrum Disorders: History, Diagnosis, Neurobiology, Treatment and Outcome*, The Biomedical And Life Sciences Collection, Henry Stewart Talks Ltd, London (Online At [Http://Hstalks.Com.Abc.Cardiff.Ac.Uk/Bio](http://Hstalks.Com.Abc.Cardiff.Ac.Uk/Bio))

Van Den Veyer, I.B. and Zoghbi, H.Y. (2002). Genetic basis of Rett syndrome. *Mental Retardation and Developmental Disabilities Research Review*, 8, 82-86.

Verri, A.P., Maraschio, P., Uggetti, C., Pucci, E., Ronchi, G., Nespoli, L., Destefani, V., Romponi, A. and Federico, A. (2004). Late diagnosis in severe and mild intellectual

disability in adulthood. *Journal of Intellectual Disability Research*, 48, 679-686.

Vignoli, A., La Briola, F. and Canevini, M. (2009). Evolution of stereotypes in adolescents and women with Rett syndrome. *Movement Disorders*, 24, 1379-83.

Vignoli, A., Fabio, R., La Briola, F., Giannatiempo, S., Antonietti, A., Maggiolini, S. and Canevini, M. (2010). Correlations between neurophysiological, behavioral, and cognitive function in Rett syndrome. *Epilepsy & Behaviour*, 17, 489-96.

Vignoli A., La Briola F., Peron A., Turner K., Savini M., Cogliati F., Russo S., Canevini M. P. (2012). Medical care of adolescents and women with Rett syndrome: An Italian study. *American Journal of Medical Genetics Part A*, 158A, 13 – 18.

Von Tetzchner, S., Jacobsen, K., Smith, L., Skjeldal, O., Heiberg, A. and Fagan, J. (1996). Vision, cognition and developmental characteristics of girls and women with Rett syndrome. *Developmental Medicine and Child Neurology*, 38, 212-25.

Von Tetzchner, S. (1997). Communication skills among females with Rett syndrome. *European Child And Adolescent Psychiatry*, 6 Suppl 1, 33-7.

Vorsanova, S.G., Demidova I.A., Ulas V.Y., Soloviev K., Azantzeva, L.Z. and Yurov, Y.B. (1996). Cytogenic and molecular-cytogenic investigation of Rett syndrome: Analysis of 31 cases. *Neuroreport*, 8, 187-189.

Wales, L., Charman, T. and Mount, R. (2004). An analogue assessment of repetitive hand behaviours in girls and young women with Rett syndrome. *Journal of Intellectual Disability Research*, 48, 672-8.

Watson, J.S., Marcy, S. and Al., E. (1996). Behavioral competition in a case of Rett syndrome. *Journal of Applied Developmental Psychology*, 17, 553-575.

Watson, J.S., Umansky, R., Marcy, S. and Repacholi, B. (1996). Intention and preference in a 3-year-old girl with Rett syndrome. *Journal of Applied Developmental Psychology*, 17, 69-84.

Watson, P., Black, S., Barrow, M., Super, M., Kerr, B. and Clayton-Smith, J. (2001). Angelman syndrome phenotype associated with mutations in *MECP2*, a gene encoding

a Methyl-CpG Binding protein. *Journal of Medical Genetics*, 38, 224 – 228.

Weaving, L.S., Ellaway, C. J., Gecz, J. and Christodoulou, J. (2008). Rett syndrome: Clinical review and genetic update. *Journal of Medical Genetics*, 42, 1-7.

Webb T. and Latif F. (2001). Rett syndrome and the *MECP2* gene. *Journal of Medical Genetics*, 38, 217-223.

Wehmeyer, M., Bourland, G. and Ingram, D. (1993). An analogue assessment of hand stereotypies in two cases of Rett syndrome. *Journal of Intellectual Disability Research*, 37, 95-102.

Weiss J.A., Sullivan A. and Diamond T. (2003). Parent stress and adaptive functioning of individuals with developmental disabilities. *Journal of Developmental Disabilities*, 10, 129 – 136.

Weiss, J.A. and Lunskey, Y. (2012). The Brief Family Distress Scale: A measure of crisis in caregivers of individuals with autism spectrum disorders. *Journal of Child and Family Studies*, 20, 521 – 528.

Wellesley, D., Hockey, A. and Stanley, F. (1991). The aetiology of intellectual disability in Western Australia: A community-based study. *Developmental Medicine and Child Neurology*, 33, 963-973.

Wesecky, A. (1986). Music therapy for children with Rett syndrome. *American Journal of Medical Genetics*, 24, 253-257.

Whitaker, S., Walker, T. and McNally, C. (2004). The use of time base lag sequential analysis to look at the relationship between environmental events and challenging behaviour in people with learning disabilities. *Behavioural and Cognitive Psychotherapy*, 32, 67 – 76.

Wigram, T. and Lawrence, M. (2005). Music therapy as a tool for assessing hand use and communicativeness in children with Rett syndrome. *Brain & Development*, 27 Suppl 1, S95-S96.

Wing, L., Leekam, S.R., Libby, S.J, Gould, J. and Locombe, M. (2002). The Diagnostic Interview for Social and Communication Disorders: Background, inter-rater reliability and clinical use. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 43, 307 – 325.

Witt-Engerstrom (1987). Rett syndrome: A retrospective pilot study on potential early predictive symptomatology. *Brain & Development*, 9, 481 – 486.

Witt-Engerstrom I. (1992). Rett syndrome: The late infantile regression period – A retrospective analysis of 91 cases. *Acta Paediatrica*, 81, 167-172.

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

Woodyatt, G. and Ozanne, A. (1993). A longitudinal study of cognitive skills and communication behaviours in children with Rett syndrome. *Journal of Intellectual Disability Research*, 37, 419-35.

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

Woodyatt, G. and Murdoch, B. (1996). The effect of the presentation of visual and auditory stimuli on the breathing patterns of two girls with Rett syndrome. *Journal of Intellectual Disability Research*, 40, 252-9.

Woodyatt, G. and Ozanne, A. (1997). Rett syndrome and profound intellectual disability: cognitive and communicative similarities and differences. *European Child and Adolescent Psychiatry*, 6, 31-2.

Woodyatt, G. and Sigafos, J. (2000). Effects of amount and type of social interaction/activity on stereotyped hand mannerisms in individuals with Rett syndrome. *Australasian Journal of Special Education*, 23, 15-24.

Woodyatt G., Marinac, J., Darnell, R., Sigafos, J. and Halle, J. (2004). Behaviour state analysis in Rett syndrome: continuous data reliability measurement. *International*

*Journal of Disability, Development and Education*, 51, 383-400.

World Health Organisation (1992). ICD-10 Classification of Mental and Behavioural Disorders: Clinical Description and Diagnostic Guideline. Geneva: WHO

Wright, M., Van Der Linden, M. L., Kerr, A. M., Burford, B., Arrowsmith, G. and Middleton, R. L. (2003). Motion analysis of stereotyped hand movements in Rett syndrome. *Journal of Intellectual Disability, Research*, 47, 85-89.

Wulffaert, J., Van Berckelaer-Onnes, I. and Scholte, E. (2009a). Autistic disorder symptoms in Rett syndrome. *Autism*, 13, 567-81.

Wulffaert, J., Van Berckelaer-Onnes, I., Kroonenberg, P., Scholte, E., Bhuiyan, Z. and Hennekam, R. (2009b). Simultaneous analysis of the behavioural phenotype, physical factors, and parenting stress in people with Cornelia de Lange syndrome, *Journal of Intellectual Disability Research*, 53, 604 – 619.

Wylie, M. (1996). A case study to promote hand use in children with Rett syndrome. *Music Therapy Perspectives*, 14, 83-86.

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

Yoder, P.J, Feurer, I.D. (2000). Quantifying the magnitude of sequential association between events or behaviors. In: Thompson, T., Felce, D., *Behavioral observation: Technology and application in developmental disabilities*. Baltimore: Brookes; pp. 317–333.

Yoder, P.J., Bruce, P. and Tapp, J. (2001). Comparing sequential associations within a single dyad. *Behavior Research Methods, Instruments & Computer*, 33, 331 – 338.

Young, D., Nagarajan, L., De Klerk, N., Jacoby, P., Ellaway, C. and Leonard, H. (2007). Sleep problems in Rett syndrome. *Brain & Development*, 29, 609-16

Young, D., Bebbington, A., Anderson, A., Ravine, D., Ellaway, C., Kulkarni, A., De Klerk, N., Kaufmann, W. and Leonard, H. (2008). The diagnosis of autism in a female:

Could it be Rett syndrome? *European Journal of Pediatrics*, 167, 661-9.

Zappella, M. (1986). Motivational conflicts in Rett syndrome. *American Journal Of Medical Genetics*, Supplement 1, 143-51.

Zigmomd, A.S., and Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatric Scandinavia*, 67, 361-37

**APPENDIX A – DIAGNOSTIC CRITERIA FOR RETT SYNDROME  
(HAGBERG ET AL. 2002)**

**Appendix A - 1: Classic Rett Syndrome Rett Syndrome Diagnostic Criteria,  
(Hagberg et al. 2002)**

**Necessary criteria**

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Apparently normal prenatal and perinatal history

Psychomotor development largely normal through the first 6 months or may be  
delayed from birth

Normal head circumference at birth

Postnatal deceleration of head growth in the majority

Loss of achieved purposeful hand skills between ages  $\frac{1}{2}$  -2  $\frac{1}{2}$  years

Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping,  
mouthing and washing/rubbing automatisms.

Emerging social withdrawal, communication dysfunction, loss of learned words,  
and cognitive impairment

Impaired (dyspraxic) or failing locomotion

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**Supportive criteria**

1. Awake disturbances of breathing (hyperventilation, breath-holding, forced expulsion of air or saliva, air swallowing)
2. Bruxism
3. Impaired sleep pattern from early infancy
4. Abnormal muscle tone successively associated with muscle wasting and dystonia
5. Peripheral vasomotor disturbances
6. Scoliosis/kyphosis progressing through childhood
7. Growth retardation
8. Hypotrophic small and cold feet; small, thin hands

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**Exclusion criteria**

- Organomegaly or other signs of storage disease
  - Retinopathy, optic atrophy, or cataract
  - Evidence of perinatal or postnatal brain damage
  - Existence of identifiable metabolic or other progressive neurological disorder
  - Acquired neurological disorders resulting from severe infections or head trauma
-

## **Appendix A - 2 Diagnostic Criteria for atypical or variant form of Rett Syndrome (Hagberg et al. 2002)**

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At least 3 of the 6 main criteria

At least 5 of the 11 supportive criteria

### **Main criteria**

6. Absence or reduction of hands skills
7. Reduction or loss of speech (including babble)
8. Hand stereotypies
9. Reduction or loss of communication skills
10. Deceleration of head growth from early childhood
11. Regression followed by recovery of interaction

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### **Supportive criteria**

1. Breathing irregularities
  2. Air swallowing or abdominal bloating
  3. Bruxism
  4. Abnormal locomotion
  5. Scoliosis or kyphosis
  6. Lower limb amyotrophy
  7. Cold, discolored feet, usually hypotrophic
  8. Sleep disturbances, including night time screaming
  9. Inexplicable episodes of laughing or screaming
  10. Apparently diminished pain sensitivity
  11. Intense eye contact and/or eye pointing
-

**APPENDIX B**  
**LITERATURE REVIEW TABLES**

## Appendix B – 1: List of studies excluded from literature review

1. Bashina, N.V., Simashkova, V.V., Grachev, N.L. and Gorbachevskaya, N.L. (2002). Speech and motor disturbances in Rett syndrome. *Neuroscience and Behavioral Physiology*, 32, 323-327. (Clinical study)
2. Bergstrom-Isacson M., Julu P. and Witt-Engestrom I. (2007). Autonomic responses to music and vibroacoustic therapy in Rett syndrome. A controlled within-subject study. *Nordic Journal of Music Therapy*, 16, 42-59 (Multiple case study design)
3. Budden, S., Meek, M. and Henigham, C. (1990). Communication and oral-motor function in Rett syndrome. *Developmental Medicine & Child Neurology*, 32, 51-55 (Adaptive skills)
4. Bumin G., Uyanik M., Kayihan H., Duger T. and Topcu M. (2002). The effect of hand splints on stereotypic hand behavior in Rett's syndrome. *Turkish Journal of Pediatric*, 44, 25 - 29 (Intervention program)
5. Burford, B. and Trevarthen, C. (1997). Evoking communication in Rett syndrome: comparisons with conversations and games in mother-infant interaction. *European Child & Adolescent Psychiatry*, 6, 26-30. (No empirical study)
6. Downs J., Bebbington, A., Jacoby, P., Williams, A.M., Ghosh S., Kaufmann, W. and Leonard, E. (2010). Level of purposeful hand function as a marker of clinical severity in Rett syndrome. *Developmental Medicine & Child Neurology*. (Explore hand functions)
7. Downs, J. A., Bebbington, A., Jacoby, P. Msall, M. E., McIlroy, O., Fyfe, S., Bahi-Buisson, N., Kaufmann, W. E. and Leonard, H. (2008). Gross motor profile in Rett syndrome as determined by video analysis. *Neuropediatrics*, 39, 205-210. (Clinical study - Explore motor abilities)
8. Downs, J., Bebbington, A., Kaufmann, W.E. and Leonard, H. (2011). Longitudinal hand function in Rett syndrome. *Journal of Child Neurology*, 26, 334-340 (Explore hand function)
9. Elefant C. and Wigram T. (2005). Learning ability in children with Rett syndrome. *Brain & Development*, 27, S97-S101 (Communication intervention study)

10. Elia, M. and Rudolf, N.D. (1989). Rett syndrome: Some behavioural aspects and an overview. *Behavioural Neurology*, 2, 211-218. (Review)
11. Elia, M. and Rudolf, N.D (1991). EEG and respiration in Rett syndrome. *Acta Neurologica Scandinavica*, 83, 123-128 (clinical study)
12. Fabio, R.A., Giannatiempo, S., Antonietti, A. and Budden, S. (2009a). The role of stereotypies in overselectivity process in Rett syndrome. *Research in Developmental Disabilities*, 30, 136-145
13. Fabio, R.A., Antonietti, A., Castelli, I. and Marchetti, A. (2009b). Attention and communication in Rett syndrome. *Research in Autism Spectrum Disorder*, 3, 329-335
14. FitzGerald P. M., Jankovic J. and Percy A. K (1990). Rett syndrome and associated movement disorders. *Movement Disorders*, 5, 195-202. (Clinical cases study).
15. Fontanesi, J. and Haas, R. (1988). Cognitive Profile Of Rett Syndrome. *Journal Of Child Neurology*, 3, S20-4. (Adaptive skills)
16. Gillberg, C. (1986). Autism and Rett syndrome: some notes on differential diagnosis. *American Journal of medical Genetics*, 24, 127-131 (clinical observation)
17. Glaze D. G., Percy A. K., Skinner S., Motil K. J., Neul J. L., Barrish J. O., Lane J. B., Geerts S. P., Annese F., Graham J., McNair L. and Lee H. S. (2010). Epilepsy and the natural history of Rett syndrome. *Neurology*, 74, 909-12 (Clinical study)
18. Glaze, D., Schultz, R. and Frost, J. (1998). Rett syndrome: characterization of seizures versus non-seizures. *Electroencephalographic Clinical Neurophysiology*, 106, 79-83. (Clinical study of epilepsy)
19. Hetzroni O. and 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 (Communication intervention program)
20. Huppke P., Held M., Hanefeld F., Engel W. and Laccone F. (2002). Influence of mutation type and location on phenotype in 123 patients with Rett syndrome. *Neuropediatrics*, 33, 63-68 (Genetic study)

21. Iwata, B.A., Pace, G.M., Willis, K.D., Gamache, T.B. and Hyman, S.L. (1986). Operant studies of self-injurious hand biting in the Rett syndrome. *American Journal of Medical Genetics*, 24, 157-166 (single case study design)
22. Kerr, A., Southall, D., Amos, P., Cooper, R., Samuels, M., Mitchell J. and Stephenson, J. (1990). Correlation of electroencephalogram, respiration and movement in the Rett syndrome. *Brain & Development*, 12, 61-8 (Clinical study)
23. Kerr, A. M., Archer, H. L., Evans, J. C., Prescott, R. J. and Gibbon, F. (2006). People with MECP2 mutation-positive Rett disorder who converse. *Journal of Intellectual Disability Research*, 50, May 386-394 (Genetic study)
24. Kerr, A.M., Montague, J. and Stephenson, J.B. (1987). The hands, and the mind, pre- and post-regression, in Rett syndrome. *Brain & Development*, 9, 487-90 (Clinical study).
25. Koppenhaver, D. A., Erickson, K. A., Harris, B., McLellan, J., Skotko B. G. and Newton R.A. (2001). Storybook-based communication intervention for girls with Rett syndrome and their mothers. *Disability and Rehabilitation: An International, Multidisciplinary Journal*, 23,149-159. (Communication Intervention program)
26. Koppenhaver, D.A, Erickson, K.A, Harris, B, McLellan, J, Skotko, B.G. and Newton, R.A. (2001). Storybook-based communication intervention for girls with Rett syndrome and their mothers. *Disability and Rehabilitation*, 23, 149-159 (Communication Intervention study)
27. Larsson, G. and Witt Engerstrom I. (2001). Gross motor ability in Rett syndrome - the power of expectation, motivation and planning. *Brain & Development*, 23, S77-S81. (Intervention treatment)
28. Leonard, H., Fyfe, S., Leonard, S. and Msall, M. (2001). Functional status, medical impairments, and rehabilitation resources in 84 females with Rett syndrome: a snapshot across the world from the parental perspective. *Disability and Rehabilitation*, 23, 107-117 (Family wellbeing study).
29. McArthur, A. J. and Budden, S. S. (1998). Sleep dysfunction in Rett syndrome: A trial of exogenous melatonin treatment. *Developmental Medicine & Child Neurology*, 40, 186-192 (Clinical intervention)

30. Morton, R. E., Bonas, R., Minford, J., Tarrant, S. C. and Ellis, R. E. (1997). Respiration patterns during feeding in Rett syndrome. *Developmental Medicine & Child Neurology*, 39, 607-13 (Clinical study exploring feeding)
31. Morton, R. E., Pinnington, L. and Ellis, R. E. (2000). Air swallowing in Rett syndrome. *Developmental Medicine & Child Neurology*, 42, 271-5 (Clinical study reporting air swallowing)
32. Naganuma, G.M. and Billingsley, F.F. (1988). Effect of hand splints on stereotypic hand behavior of three girls with Rett syndrome. *Physical Therapy*, 68, 664-71 (Intervention program)
33. Oliver, C., Murphy, G. and Crayton, L. (1993). Self-injurious behavior in Rett syndrome: interaction between features of Rett syndrome and operant conditioning. *Journal of Autism and Developmental Disabilities*, 23, 91-109 (Single case study design)
34. Percy A., Gillberg C., Hagberg B. and Witt Engerstrom I. (1990). Rett syndrome and the autistic disorder. *Neurologic Clinics*, 8, 659-676 (Review)
35. Perry, A., Sarlo-Mcgarvey, N. and Haddad, C. (1991). Brief Report: Cognitive and adaptive functioning in 28 girls with Rett syndrome. *Journal of Autism Developmental Disorders*, 21, 551-6. (Adaptive skills)
36. Pintaudi, M., Calevo, M.G., Vignoli, A., Parodi, E., Aiello, F., Baglietto, M. G., Hayek, Y., Buoni, S., Renieri, A., Russo, S., Cogliati, F., Giordano, L., Canevini, M.P. and Veneselli, E. (2010). Epilepsy in Rett syndrome: Clinical and genetic features. *Epilepsy & Behavior*, 19, 296-300 (Clinical study)
37. Ryan, D., McGregor, F., Akermanis, M., Southwell, K., Ramke, M. and Woodyatt, G. (2004). Facilitating communication in children with multiple disabilities: three cases studies of girls with Rett syndrome. *Disability and Rehabilitation*, 26, 1268-1277 (Intervention study)
38. Roane, H. S., Piazza, C. C., Sgro, G. M., Volkert, V. M. and Anderson, C. M., (2001). Analysis of aberrant behaviour associated with Rett syndrome. *Disability and Rehabilitation*, 23, 139-148 (Intervention study)
39. Sandberg, A. D., Ehlers, S., Hagberg, B. and Gillberg, C. (2000). The Rett Syndrome complex: Communicative functions in relation to developmental level and autistic features. *Autism*, 4, 249-267. (Multiple case study design)

40. Sharpe, P. A. (1992), Comparative effects of bilateral hand splints and an elbow orthosis on stereotypic hand movements and toy play in two children with Rett syndrome. *The American Journal of Occupational Therapy*, 42, 134 - 140 (Intervention program).
41. Sharpe, P. A. and Ottenbacher K. J. (1990). Use of an elbow restraint to improve finger-feeding skills in a child with Rett syndrome. *American Journal of Occupational Therapy*, 44, 328-332. (Intervention program)
42. Sigafos, J., Laurie, S. and Pennell, D. (1996). Teaching children with Rett syndrome to request preferred objects using aided communication: Two preliminary studies. *AAC: Augmentative and Alternative Communication*, 12, 88-96 (Communication Intervention study)
43. Skotko, B. G. and Erickson K. A. (2004). Parent reading behaviors and communication outcomes in girls with Rett syndrome. *Exceptional Children*, 70, 145-166 (Communication Intervention study)
44. Smith, T, Klevstrand, M. and Lovaas, O. I (1995). Behavioral treatment of Rett's disorder: Ineffectiveness in three cases. *American Journal on Mental Retardation*, 100, 317-322. (Behavioural intervention)
45. Tams-Little, S. and Holdgrafer, G. (1996). Early communication development in children with Rett syndrome. *Brain & Development*, 18, 376-378 (pre-regression)
46. Trevarthen, C. and Daniel, S. (2005). Disorganized rhythm and synchrony: early signs of autism and Rett syndrome. *Brain & Development*, 27, S25-S34 (Focus on autism)
47. Umansky, R. and Watson, J. (1998). Influence of eye movements on Rett stereotypies: Evidence suggesting a stage-specific regression. *Journal of Child Neurology*, 13, 158-62.
48. Umansky, R., Watson, J., Colvin, L., Fyfe, S., Leonard, S., De Klerk, N. and Leonard, H. (2003). Hand preference, extent of laterality, and functional hand use in Rett syndrome. *Journal of Child Neurology*, 18, 481-487.
49. Vignoli, A., Fabio, R., La Briola, F., Giannatiempo, S., Antonietti, A., Maggiolini, S. and Canevini, M. (2010). Correlations between neurophysiological, behavioral, and cognitive function in Rett syndrome. *Epilepsy and Behaviour*, 17, 489-96.

50. Von Tetzchner, S., Jacobsen, K.H., Smith, L., Skjedal, O., Helberg, A. and Fagon, J.F. (1996). Vision, cognition and developmental characteristics of girls and women with Rett syndrome. *Developmental Medicine and Child Neurology*, 38, 212-225
51. Wales, L., Charman, T. and Mount, R. (2004). An analogue assessment of repetitive hand behaviours in girls and young women with Rett syndrome. *Journal of Intellectual Disability Research*, 48, 672-678
52. Watson, J S., Umansky, R, Marcy, S. and Repacholi, B. (1996). Intention and preference in a 3-year-old girl with Rett syndrome. *Journal of Applied Developmental Psychology*, 17, 69-84. (Case study)
53. Watson, J.S. and Marcy, S. (1996). Behavioral competition in a case of Rett syndrome. *Journal of Applied Developmental Psychology*, 17, 553-575 (Intervention program)
54. Wehemeyer, M., Bourland, G. and Ingram, D. (1993). An analogue assessment of hand stereotypies in two cases of Rett syndrome. *Journal of Intellectual Disability Research*, 37, 95-102
55. Wigram, T. and Lawrence, M (2005). Music therapy as a tool for assessing hand use and communicativeness in children with Rett Syndrome. *Brain & Development*, 27, S95-S96 (Case report)
56. Woodyatt, G. C., Darnell, R. and Halle, J. (2004). Behaviour state analysis in Rett Syndrome: Continuous data reliability measurement. *International Journal of Disability, Development and Education*, 51, 383-400 (explore reliability of measurement rather than behaviour itself)
57. Woodyatt, G. C. and Ozanne, A. (1994). Intentionality and communication in four children with Rett syndrome. *Australia and New Zealand Journal of Developmental Disabilities*, 19, 173-183
58. Woodyatt, G. C. and Murdach, B. E. (1996). The effect of the presentation of visual and auditory stimuli on the breathing patterns of two girls with Rett syndrome. *Journal of Intellectual Disability Research*, 40, 252-259
59. Woodyatt, G.C. and Ozanne, A. (1997). Rett syndrome and profound intellectual disability: cognitive and communication similarities and differences. *European Child and Adolescent Psychiatry*, 6, 31 – 32 (not able to obtain from library)

60. Wright, M., Van Der Linden, M. L., Kerr, A. M., Burford, B., Arrowsmith, G. and Middleton, R. L. (2003), Motion analysis of stereotyped hand movements in Rett syndrome. *Journal Of Intellectual Disability, Research*, **47**, 85-89
61. Zappella, M. (1985). Rett syndrome – A significant proportion of girls affected by autistic behavior. *Brain & Development*, 73, 307-312 (Clinical report)
62. Zappella, M. (1986). Motivational conflicts in Rett syndrome. *American Journal of Medical Genetics*, 24, 143-151 (Clinical report)

## Appendix B – 2: Standardised measures used in Rett syndrome behavioural phenotype studies

Measure	Age range	Respondent	Focus of measure	Studies
Aberrant Behavior Checklist (Aman and Singh 1994)	All ages	Parent, carer	Assesses behavioural problems through 58 items rated on a 4-point scale, 0 to 3. Produces 5 subscales: Irritability, Lethargy, Stereotypy, Hyperactivity, Inappropriate Speech.	Mount et al. 2002a
Adaptive Behavior Scale -School (Lambert et al. 1993)	Children 6-14 yrs.	Observational rating scale	Assesses behaviour and social adjustment.	Hetzroni and Rubin 2006
Autism Behavior Checklist (Krug et al. 1980)	All ages	Parent	Part of the Autism Screening Instrument for Educational Planning (ASIEP). It consists of 57 items subdivided into 5 subscales: Sensory, Body & Objects Use, Language, Social & Self-help.	Mount et al. 2003b
Autism Spectrum Disorder – Problem Behavior Adult (Matson et al. 2007)	Adult	Parent, teacher, carer	Assesses problem behaviour in three domains: aggressive/destructive, self-injurious and disruptive behaviour. Contains 20 items	Matson et al. 2008
Developmental Behaviour Checklist (Einfield and Tongue 1992)	All ages	Parent, teacher, carer	Assesses behavioural and emotional problems over a 6-month period in individuals with developmental and intellectual disabilities.	Wulffaert et al. 2009; Mount et al. 2003a
Diagnostic Interview for Social and Communication Disorders (Wing et al. 2002)	All ages	Parent, teacher, carer	Semi-structured interview for the diagnosis of autism and related disorders.	Wulffaert et al. 2009
Inventory of Potential Communicative Acts (Sigafoos et al. 2000a)	All ages	Observation	Assess the function of communicative behaviours in 10 categories: Social convention, Attention to self, Reject/protest, Request an object, Request an action, Request information, Comment, Choice making, Answer, Imitation	Dibben et al. 2010; Hetzroni and Rubin 2006; Sigafoos et al. 2000b
Matson Evaluation of Social Skills for Individuals with Severe Retardation (Matson et al. 1998)	Adult	Parent, carer	Assesses positive and negative social behaviour through 85 items rated on a 4 point scale: 0- never, 1- rarely, 2- some, 3- often.	Matson et al. 2008
Modified Uzgiris and Hunt Scale of Infant Psychological Development (Dunst 1980)	Children	Test with child	Assesses child sensory-motor development in six Piaget categories: Objects performance, Means-end abilities, Vocal imitation, Gestural imitation,	Woodyatt and Ozanne 1992, 1993

Operationally causality, Construct of objects in space				
Non-speech Test (Huer 1983)	0-4 yrs.	Test, observation	Designed for evaluation of students with communication disabilities.	Hetzroni and Rubin 2006
Observational Tool for Analysing the Communicative Functions of Aberrant Behaviours (Donneland et al. 1984)	All ages	Observation	Assesses possible functions of communicative acts.	Woodyatt and Ozanne 1992, 1993; Sigafoos et al. 2000b
Rett Syndrome Behavioural Questionnaire (Mount et al. 2002b)	All ages	Parent, carer	Assess RTT specific behavioural and emotional features using 8 subscales: General Mood, Hand behaviour, Breathing Abnormalities, Repetitive Face movements, Body Rocking and Expressionless Face, Night-Time behaviours, Fear/Anxiety and Walking/Standing.	Mount et al. 2002b Matson et al. 2008 Robertson et al. 2006 Kauffman et al. 2011
Screen for Social Interaction (Ghuman et al. 1998)	Infant 30-60 months	Parent	Developed to assess problems with social interaction in young children. It consists of 54 items scored on 4 points scale. Lower score indicated slower or delay development and higher score indicated normal development.	Kauffman et al. 2011
Vineland Adaptive Behavior Scale (Sparrow et al. 1984)	0-18 yrs	Parent, teacher, carer	Assess adaptive behaviour in four domains: Communication, Daily living skills, Socialization, Motor skills	Kauffman et al. 2011
Vineland Screener (Scholte et al. 2008)	0-6 yrs	Parent, teacher, carer	Dutch adaptation of the VABS.	Wulffaert et al. 2009

### Appendix B – 3: Summary of behavioural and emotional characteristics of RTT

Authors	Sample characteristics	Methods	Design	Behaviour	Findings
Cirignotta et al. 1986	4 females 8-21 Yrs	Polygraphic recording during wakefulness and during spontaneous sleep.	Cross sectional	Breathing abnormalities	All cases had irregular breathing pattern during wake, in particular during period of anxiety. Breathing was stable during sleep and quiet wakefulness. Breathing abnormalities included apnea and hyperventilation.
Gillberg 1987	8 children Age 3-9 yrs	Questionnaire	Retrospective study	Autistic features	Early symptoms concerned mostly items regarding sleep problems, overjoyed when tickled, day/periods when perform worst and not attracting attention when left alone. Symptoms typically found in children with autism were not common in the RTT group. These concern items such as play only with hard objects, does not like to be disturbed in her own world and pleased when left completely to herself.
Woodyatt and Ozanne 1992	6 females Age 2.5 -13.6 yrs 3 each Stage III-IV	Observation Parents and teachers interview Cognitive assessment	Cross sectional	Communication skills	Communication and comprehension skills were severely impaired in all subjects. The subjects showed poor eye contact and little awareness of presence of others. Touching and eye gaze were the communicative act observed most frequently.
Woodyatt and Ozanne 1993	6 females Age 2.6-13.7 yrs	Observation Cognitive assessments Parent/carer interview	Longitudinal	Communication skills	Communication skills remained at the pre intentional level for all 6 subjects over 3 years. 5 subjects showed some improvement in social interaction.
Elian 1996	25 female	Telephone interview	Cross sectional	Hand stereotypies and breathing abnormalities	Great variety of hand stereotypies were present in this sample with 40% being asymmetrical non midline. 20% of the sample had infrequent hand movements. 72% of parents reported a correlation between hand movements and hyperventilation either by compensating or complement each other.
Von Tetzchner 1997	42 females Age 2 ½-47 yrs	Semi-structured interview	Cross sectional	Communicative behaviours	22 girls did not have any verbal speech abilities (including non verbal communication abilities) and 17 had between 1-10 words. 39 were reported to looks at objects and 21 to use eye gaze. 11 did not have any words before regression.
Sigafoos et al. 2000b	3 females Age 10.6,18.5, 19.5 yrs	Structured interview Videotaped observations under high vs low attention. Structured probes to assess communication.	Observational	Communicative behaviours	All 3 subjects engaged in several topographies of behaviour. Stereotyped hand movements and eye gaze was high in all 3 subjects in the probes trials, but results were
Lavas et al. 2006	125 females Age 2.5-55 yrs	Parental questionnaire	Cross sectional	Communication skills and eating abilities	Communication was impaired in all sample with only 23 female reported to use words. Motor acts were the most common way to communicate (90%) and communicative behaviour was mostly reported during social activities.
Hetzroni and 2006	8 females Age 4-11 yrs	ABS-S IPCA	Cross-sectional	Communicative behaviours	Eye gaze was the most consistent behaviour showed by the girls across all

Rubin 2006	Classic RTT	Non-Speech test Staff interview Experimental communication protocol	and observatic n		situations, in contrast with other communicative behaviour that differs between the girls and activity. Eye gazing and stereotypical hand movements significantly increased in 7 girls when an activity was interrupted. Switch use, eye persistence and touching decreased once the activity was interrupted.
Baptista et al. 2006	7 females Age range 4.1- 9.6 yrs	Eye tracking technology	Cross- sectional	Communicative skills	The girls spent an average of 3.344 s looking at the computer screen, and the rest 1.656 s looking away and making head movements. The girls consistently responded to tasks such as matching pairs and categorization of objects, spending more time in the right choice.
Rohdin et al. 2008	12 female 7-20 years Classic (8), variant (1) and Congenital (3) Stage III (7)-IV (2)-III & IV (3)	Respiratory monitoring for 1 week in the home environment.	Cross sectional	Breathing abnormalities	Total recording for all patients was 1114 hour (535 during wake and 579 during sleep). Cardiorepiratory disturbance were present during wake and sleep and there were marked differences between the girls and in the same girls depending on the activity in the cardiorespiratory disturbances.
Wulffaert et al. 2009	52 female Age 2.4- 49.3 yrs 41 Classical, 10 Atypical, 1 unknown.	DBC -P DISCO-10 VS-0-6	Cross sectional	Autistic features	42% of subject score above cut off in the DBC, meaning that they exhibited behaviours which related to ASD. Younger subjects score higher (mean 18.8) than the older group (mean 13.7). 58% of the sample had a classification of Childhood Autism in the DISCO, although 19% of the sample that previously could be classified as CA did not met this criteria anymore, meaning that there is a difference between age.
De Lima Velloso et al. 2009	10 females Age 4.8 to 12.10 yrs Clinical stage III (8) or IV (2)	Ocular tracking to evaluate the recognition of the concept of colors (red, blue and yellow), shape (square, circle, triangle) and position (over and under).	Cross- sectional	Cognitive skills	Percentage of errors in recognition of concepts was significant higher than the percentage of correct answer in 9 girls.
Dibben et al. 2010	120 females Age range 5-55 yrs 60 Classic, 28 atypical and 32 unknown RTT.	Questionnaire	Cross- sectional	Communicative skills	Most common communicative acts were eye contact/gazing and laughing/smiling. Only 15% of the sample used words/speech for requesting. Functions of the communicative act were request, choice and social interaction. Environment, epilepsy and age were found to be associated with presence/absence of communicative act. Significant difference between girls living at home and residential home were found in laughing/smiling, eye contact/gazing, and vocalizations.

**APPENDIX C**  
**ETHICAL LETTERS AND RESEARCH INSTRUMENTS**

**Appendix C – 1: Ethical Approval letters**



Canolfan Gwasanaethae  
Busnes  
Business Services  
Centre

*Research Ethics Committee for Wales*  
*Ymchwil Ethegau Aml-Ganolfan yng*  
*Nghymru*

*4 Llawr, Ty Churchill*  
*17 Ffordd Churchill*  
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*Fourth Floor, Churchill House*  
*17 Churchill Way*  
*Cardiff, CF10 2TW*

*Telephone : 029 2037 6829*

*Fax : 029 2037 6824*

25 February 2010

Mrs Rina Cianfaglione  
PhD student  
Cardiff University  
Neuadd Meirionnydd  
Heath Park  
Cardiff CF14 4YS

Dear Mrs Cianfaglione

**Study title:** Behavioural phenotypes and the support needs of girls and women with Rett Syndrome and their families.  
**REC reference:** 09/MRE09/50  
**Amendment number:** Amendment 1 dated February 2010  
**Amendment date:**

The above amendment was reviewed at the meeting of the Sub-Committee held on 25 February 2010

#### Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

#### **Approved documents**

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Consent Form: Family consent form : direct observation	3 dated February 2010	
Participant Information Sheet: Part Two : Direct Observation	3 dated February 2010	
Notice of Substantial Amendment (non-CTIMPs)	Amendment 1	

	dated February 2010	
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**Membership of the Committee**

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

<b>.09/MRE09/50: correspondence</b>	<b>Please quote this number on all</b>
---	--

Yours sincerely

**Dr. Corinne Scott**

Committee Co-ordinator

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr K J Pittard Davies, Cardiff University

**REC for Wales**

**Attendance at Sub-Committee of the REC meeting on 25 February 2010**

Name	Profession	Capacity
Dr Maurice Buchalter	Alternate Vice Chairman / Hospital Consultant (Cardiologist)	Expert
Mr Keith Jones	Retired Probation Officer	Lay
Dr Gordon Taylor	Chairman / Statistician	Expert
Dr Pete Wall	Vice Chairman / Clinical	Expert

	Physiologist	
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**Also in attendance:**

Name	Position (or reason for attending)
Dr Corinne Scott	Co-ordinator

Research Ethics  
Committee for Wales

# REC for WALES

Ymchwil Ethegau  
Aml-Ganolfan  
yng Nghymru

Administrator/Gweinyddes:  
Dr. Corinne Scott

Churchill House, Fourth Floor, 17 Churchill Way, Cardiff, CF10 2TW  
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Fax No. 029 2037 6824

15 February 2010

Mrs Rina Cianfaglione  
PhD student  
Cardiff University  
Neuadd Meirionnydd  
Heath Park  
Cardiff CF14 4YS

Dear Mrs Cianfaglione

**Study title:** Behavioural phenotypes and the support needs of girls and women with Rett Syndrome and their families.  
**REC reference:** 09/MRE09/50  
**Amendment number:** Amendment 1 dated February 2010  
**Amendment date:**

Thank you for submitting the above amendment, which was received on 09 February 2010. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub-Committee of the REC at its next meeting scheduled for 25 February 2010.

#### Documents received

The documents to be reviewed are as follows:

Document	Version	Date
Participant Consent Form: Family consent form : direct observation	3 dated February 2010	
Participant Information Sheet: Part Two : Direct Observation	3 dated February 2010	
Notice of Substantial Amendment (non-CTIMPs)	Amendment 1 dated February 2010	

Notification of the Committee's decision

The Committee will issue an ethical opinion on the amendment within a maximum of 35 days from the date of receipt.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval for the research.

**.09/MRE09/50:  
correspondence**

**Please quote this number on all**

Yours sincerely

**Dr. Corinne Scott**

**Appendix C – 2: Invitation letter, leaflet, consent and assent form**

**FAMILY CONSENT FORM**  
**National Survey**

**Title of the study: Support needs for Rett Syndrome**

**Name of researcher: Rina Cianfaglione**

Your name: .....

Your address: .....

.....

.....

Your telephone number .....

✓ I understand what taking part in the research project will involve

✓ I give my consent to participation in the research

I consent to the participation of my child relative (if under 18 years old)

**OR**

I give my assent to the participation of my adult relative (if 18 years or older) Please return the assent form together with this form.

**OR**

I think my adult relative may be able to give consent independently and I would like you to contact us about this.

**(Please tick one)**

✓ I will complete the questionnaire and I consent to the information being used anonymously.

✓ I consent to the British Isle Rett Syndrome Survey releasing my details to the researchers involved in this study.

✓ I consent to be contacted directly by the researchers involved in this study

✓ I know that I can change my mind and withdraw my consent at any time

✓ I know that this would not affect the care of my relative or family in any way

✓ I know that all the information collected will be kept private and that the names of participants will never be used in anything that is written about the evaluation

Signed: .....

Relationship to person with Rett Syndrome: .....

Date: .....

When complete, please return to: Rina Cianfaglione, Welsh Centre for Learning Disabilities, School of Medicine, Cardiff University, 2<sup>nd</sup> Floor Neuadd Meirionnydd, Heath Park, Cardiff, CF14 4YS

If you have any queries please ring Rina Cianfaglione 029 20687217 or David Felce 029 20687208

**FAMILY CONSENT FORM**  
**Direct Observation**

**Title of the study: Support needs for Rett Syndrome**

**Name of researcher: Rina Cianfaglione**

Your name: .....

Your address: .....

.....

.....

Your telephone number .....

- ✓ I understand what taking part in the research project will involve
- ✓ I consent to be part of the study and to be observed

I consent to the participation of my child relative (if under 18 years old)

(Please tick one)

**OR**

I give my assent to the participation of my adult relative (if 18 years or older)

**OR**

I think my adult relative may be able to give consent independently and I would like you to contact us about this.

I give my consent for my family to be video recorded.

YES  NO (small computer will be used to record events)

- ✓ I know that I can change my mind and withdraw my consent at any time
- ✓ I know that this would not affect the care of my relative or family in any way
- ✓ I know that all the information collected will be kept private and that the names of participants will never be used in anything that is written about the evaluation
- ✓ I understand that in the unlikely event that anything is observed suggesting an individual is at danger from harm, this would be passed to the highest level of seniority within the supporting service.

Signed: .....

Relationship to person with Rett Syndrome: .....

Date: .....

When complete, please return to: Rina Cianfaglione, Welsh Centre for Learning Disabilities, School of Medicine, Cardiff University, 2<sup>nd</sup> Floor Neuadd Meirionnydd, Heath Park, Cardiff, CF14 4YS

If you have any queries please ring Rina Cianfaglione 029 20687217 or David Felce 029 20687208

Dear Participant in the British Isles Rett Syndrome Survey,

Thank you for taking part in the British Isles Rett Syndrome Survey.

We are writing to you now to see if you might be willing to help with another research project on Rett syndrome. This is being carried out by our colleagues Professor David Felce and Rina Cianfaglione (a PhD research student) and aims to help us understand the behaviours of girls and women with Rett syndrome, especially those that are difficult or distressing.

As you will know, these can take very different forms and may have a range of possible causes – such as pain, boredom, epileptic seizures, disturbances in the control of breathing and simply a sense of frustration. We would like to know what might trigger a distressing episode and what we can do to make these difficult spells less frequent or easier to cope with.

In addition, we would like to find out more about the needs of carers and the wider family.

Do have a look at the project information sheet (enclosed). If you might be willing to take part, it would involve you in filling out a questionnaire in the first year of the study and again after two years. The questionnaire is long, but you can take your time to complete all the sections.

If you fill in the questionnaire, some of you will later be asked whether you might allow Rina to observe your daughter with Rett Syndrome in your family for a few hours over a couple of days. You need not agree to this - we would be delighted if you would agree to fill out the questionnaire even if you think that you would not like to be part of the observational study. We expect to send the questionnaires to lots of families but only to observe a small number.

Thank you for reading this. Do please contact Rina if you might be willing to take part so that she can tell you more about the research. (Contact details for Rina Cianfaglione and David Felce are in the information leaflet).

Sincerely,

Dr Angus Clarke,  
(Professor in Clinical Genetics)

Dr Anna Jaworska  
(Coordinator, British Isles Rett  
Syndrome Survey)

**FAMILY CONSENT FORM**  
**Direct Observation**

**Title of the study: Support needs for Rett Syndrome**

**Name of researcher: Rina Cianfaglione**

Your name: .....

Your address: .....

.....

.....

Your telephone number .....

- ✓ I understand what taking part in the research project will involve
- ✓ I consent to be part of the study and to be observed

I consent to the participation of my child relative (if under 18 years old)

(Please tick one)

**OR**

I give my assent to the participation of my adult relative (if 18 years or older)

**OR**

I think my adult relative may be able to give consent independently and I would like you to contact us about this.

I give my consent for my family to be video recorded.

YES  NO (small computer will be used to record events)

- ✓ I know that I can change my mind and withdraw my consent at any time
- ✓ I know that this would not affect the care of my relative or family in any way
- ✓ I know that all the information collected will be kept private and that the names of participants will never be used in anything that is written about the evaluation
- ✓ I understand that in the unlikely event that anything is observed suggesting an individual is at danger from harm, this would be passed to the highest level of seniority within the supporting service.

Signed: .....

Relationship to person with Rett Syndrome: .....

Date: .....

When complete, please return to: Rina Cianfaglione, Welsh Centre for Learning Disabilities, School of Medicine, Cardiff University, 2<sup>nd</sup> Floor Neuadd Meirionnydd, Heath Park, Cardiff, CF14 4YS

If you have any queries please ring Rina Cianfaglione 029 20687217 or David Felce 029 20687208

School of Medicine  
Welsh Centre for Learning Disabilities  
Professor David Felce  
Professor Michael Kerr

*Tsgol Meddygaeth*  
*Canolfan Gymreig ac gyfer Anableddau Dysgu*  
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To contact Rina Cianfaglione: Tel 029 20687217 Email [CianfaglioneR@cf.ac.uk](mailto:CianfaglioneR@cf.ac.uk)

To contact David Felce: Tel 029 20687208 Email [felce@cf.ac.uk](mailto:felce@cf.ac.uk)

## **Support needs for Rett Syndrome**

### Project Information Leaflet: Part Two Direct Observation

As you will know from your participation in the questionnaire survey, the Welsh Centre of Learning Disabilities and Cardiff Rett Syndrome Research Group, at Cardiff University, have received PhD funding from the Wales Office of Research and Development to study the support needs of people with Rett Syndrome and their families.

Rina Cianfaglione is undertaking the research with supervision from Professor David Felce (Welsh Centre for Learning Disabilities) and Professor Angus Clarke (Cardiff Rett Syndrome Research Group, Institute of Medical Genetics).

***We are now inviting you and your relative to take part in the second phase of the study, which involves observing you and your daughter in the normal course of everyday life.***

This leaflet tells you about this part of the research - to help you decide whether you would like to take part.

### Purpose of the study

Individuals with Rett Syndrome have certain behaviours and difficulties in common (e.g., loss of hand skills, loss of speech, poor communication skills, stereotyped hand movements, breathing problems, anxiety and mood changes). Abrupt changes in mood, displays of anxiety and episodes of breath holding or air swallowing cause distress to families. It is not always easy to know what triggers these events and whether there

is anything that families can do to avoid them. The aim is to observe these things happening in ordinary life and to see whether there are any patterns in how individuals respond to what is going on around them which might suggest why these events occur.

#### What would taking part involve for you

What you will experience is a researcher (Rina) coming to your home with the intention of fading into the background (being a 'fly on the wall') to video record your relative and video record what she does. Rina will also video record you and other members of the family as you do things with your daughter. We would like to get about 12 hours of observation in total - 6 hours now and another 6 hours in about a year's time. Each period of 6 hours can be spread over several days. When and for how long we observe at a time will be arranged at your convenience.

We record what is going on using a very small video camera, and we would then transfer the recording into a computer for analysis.

However if you would prefer you and your family not to be video recorded, we will record what is going on by using a small portable computer, by pressing keys that correspond to codes for behaviours and other events.

It is not normal to have someone observing what you and your family are doing so it can feel very peculiar, particularly at first. We have quite a lot of experience of doing observational research and find that people do get used to it surprisingly quickly.

#### How were you been chosen to receive this invitation to take part?

You filled in the questionnaire we sent to you last year. We hope that about 15 families will volunteer to be observed and we are contacting those who are closest to us.

#### Confidentiality

All the observational data we will collect will be kept strictly confidential.

The observational files are transferred from the video camera (or from the small computers) we use for observation into a desktop computer. They will be stored under an anonymous research code and not by any information by which you could be identified.

Access to video recording and personal information will be limited to the researchers directly involved in the study and will be kept secure. Personal information will not be passed onto anyone else.

All staff sign an undertaking to keep personal information confidential.

Reports of the results of the study will not contain personal information.

#### What will happen to the results of the study?

We will:

- send everyone who takes part a short report of our findings,
- report progress and the results of the study at meetings of the Rett Syndrome Association UK and other conferences,
- arrange a special meeting for participating families to hear what we have found if people felt that was a good idea, and
- write articles for academic and professional journals to publish the results of the research.

#### What happens next?

If you decide to take part in the study, we would like you to complete and sign the *Family Consent Form: Direct Observation*. This gives consent for your own involvement in the study and either consent for your relative's involvement if she is under 18 years of age OR your assent for your relative's involvement if she is 18 years of age or older OR your view that your adult relative may be capable of giving independent informed

consent. We will contact your relative to explain the research in this last case.

Your participation is entirely voluntary

It is entirely your decision whether to take part in the proposed study.

If you decide to do so but later change your mind, you are free to withdraw from the study at any time.

We would like to stress that your decision to participate or not will have no effect on the services you and your relative are receiving.

Thank you for taking the time to read this leaflet.

Please feel free to ask us about anything that is not clear or to contact us if you would like more information. (See letterhead for contact details).

School of Medicine  
Welsh Centre for Learning Disabilities  
Professor David Felce  
Professor Michael Kerr

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To contact Rina Cianfaglione: Tel 029 20687217 Email [CianfaglioneR@cf.ac.uk](mailto:CianfaglioneR@cf.ac.uk)

To contact David Felce: Tel 029 20687208 Email [felce@cf.ac.uk](mailto:felce@cf.ac.uk)

## **Support needs for Rett Syndrome**

### Project Information Leaflet for Individuals with Rett Syndrome

A research student, called Rina Cianfaglione, and two professors, David Felce and Angus Clarke from Cardiff University want to ask your family about how you having Rett Syndrome affects everyone in the family.

How does Rett Syndrome affect your daily life?

How do the problems you have affect the family?

What progress you have made?

What help do you and your family need?

*Question: Can you explain what we want to find out?*

We want to ask your family about you?

- what you can and cannot do
- problems you have
- how you have changed since you were young

*Questions: Who do we want to ask questions about?*

*Who do we want to answer the questions?*

We want your permission to ask your family these questions about you.

Before you decide we want you to know that:

- we will keep the information we collect private
- the information will not be linked to your name
- we will not give the information to anyone else
- your name will not be used in any report we write about the research
- we will report what we have found out to people who have taken part in the research and to other families, professionals and researchers

*Question: will your name be used when we report what we have found out?*

It is for you to decide whether to take part in the research. You do not have to agree. You should agree only if you want to take part.

If you do agree now, you can change your mind later and leave the research.

We are going to give you two weeks to think about it and discuss with other people if you want. Then we will ask you for your permission for us to ask your family about you.

School of Medicine  
Welsh Centre for Learning Disabilities  
Professor David Felce  
Professor Michael Kerr

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To contact David Felce: Tel 029 20687208 Email [felce@cf.ac.uk](mailto:felce@cf.ac.uk)

## **Support needs for Rett Syndrome**

### Project Information Leaflet for Individuals with Rett Syndrome: Part Two

#### Direct Observation

A research student, called Rina Cianfaglione, and two professors, David Felce and Angus Clarke from Cardiff University are doing research to see how you having Rett Syndrome affects everyone in the family.

We want to watch you and family at home and record what you do:

- what activities you do
- what you do when your family are with you
- when you do things that are common among people with Rett Syndrome.

Question: Can you tell us what we want to do?

The researcher will stand quietly when watching you and your family. It will be strange as the researcher will not talk to you when doing this.

The researcher will record what you are doing using a very small computer.

*Question: Can you tell us how the researcher will record what you are doing?*

We want your permission to visit you at home and watch you and your family.

Before you decide we want you to know that:

- we will keep the information we collect private
- the information will not be linked to your name
- we will not give the information to anyone else
- your name will not be used in any report we write about the research
- we will report what we have found out to people who have taken part in the research and to other families, professionals and researchers

*Question: will your name be used when we report what we have found out?*

It is for you to decide whether to take part in the research. You do not have to agree. You should agree only if you want to take part.

If you do agree now, you can change your mind later and leave the research.

We are going to give you two weeks to think about it and discuss with other people if you want. Then we will ask you for your permission for us to ask your family about you.

## **Appendix C – 3: Questionnaire packs**

School of Medicine  
Welsh Centre for Learning Disabilities  
Professor David Felce  
Professor Michael Kerr

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To contact David Felce: Tel 029 20687208 Email [felce@cf.ac.uk](mailto:felce@cf.ac.uk)

Dear

Firstly I would like to thank you for returning the consent form.

Enclosed are the questionnaire packs, part 1 and part 2.

As mentioned already in the information leaflet, you can complete the questionnaire in your own time. We have divided the packs into sections, so you can complete one at the time.

Before sending the questionnaire pack back, please check that you have completed all the questions. To help you with this there is a list in the front of the pack that you can tick once you have finished filling one questionnaire.

Once you have completed it, please return the questionnaire in the provided free post envelope (no stamp is required).

Please feel free to contact us if you would like to ask any questions about the questionnaire.

Once again, I would like to thank you to participate in the research.

Sincerely

Rina Cianfaglione



Research Number

**Support needs of Girls/Women with Rett Syndrome and their Families**

**Instructions for completing questionnaires**

12. The questionnaires should be completed by the main caregiver. You do not have to complete them all in one go. Please find time when it is convenient to you.
13. When you have completed all the questionnaires, please check that you have answered every question in each questionnaire, and return the pack to me in the pre-paid envelope provided.
14. In the pack we have included a checklist of the separate questionnaires that I have sent you. Please use this to make sure that you are returning all of the questionnaires.

***Thank you for agreeing to participate in this research and for taking the time to complete the questionnaires.***

Rina Cianfaglione  
PhD Student  
Welsh Centre for Learning Disabilities, School of Medicine, Cardiff University

# CHECKLIST OF QUESTIONNAIRES

## PART 1 YOUR CHILD WITH RETT SYNDROME

**THIS SECTION OF THE QUESTIONNAIRE ASKS QUESTIONS ABOUT THE BEHAVIOUR OF YOUR CHILD WITH RETT SYNDROME**

**PLEASE READ THE INSTRUCTIONS CAREFULLY AND COMPLETE THE FOLLOWING QUESTIONNAIRES**

**PLEASE COMPLETE THE QUESTIONNAIRES AT A TIME CONVENIENT TO YOU. YOU DO NOT HAVE TO COMPLETE THEM ALL IN ONE GO**

- |  |                          |
|--|--------------------------|
| 1. BACKGROUND INFORMATION _____                    | <input type="checkbox"/> |
| 2. YOUR CHILD DEVELOPMENT _____                    | <input type="checkbox"/> |
| 3. HEALTH QUESTIONNAIRE _____                      | <input type="checkbox"/> |
| 4. ACTIVITY QUESTIONNAIRE _____                    | <input type="checkbox"/> |
| 5. MOOD, INTEREST AND PLEASURE QUESTIONNAIRE _____ | <input type="checkbox"/> |
| 6. RETT SYNDROME BEHAVIOUR QUESTIONNAIRE _____     | <input type="checkbox"/> |
| 7. CHALLENGING BEHAVIOUR QUESTIONNAIRE _____       | <input type="checkbox"/> |
| 8. DEVELOPMENTAL BEHAVIOUR CHECKLIST _____         | <input type="checkbox"/> |
| 9. REPETITIVE BEHAVIOUR QUESTIONNAIRE _____        | <input type="checkbox"/> |

**PART 1**

**BACKGROUND INFORMATION**

**The following questions ask you about your child with Rett Syndrome**

• **Today's date:** \_\_\_\_\_

• **Your relationships to your child with Rett Syndrome:**

**MOTHER**  **FATHER**

• **Your child's date of birth:** \_\_\_/\_\_\_/\_\_\_ **Age:** \_\_\_\_\_

• **When was your daughter diagnosed?** \_\_\_\_\_

• **Who diagnosed your child:**

Paediatrician

Clinical geneticist

GP

Other \_\_\_\_\_

**6. Has a genetic cause for your child with Rett Syndrome been confirmed?**

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_ **If not known, tick box**

**7. What is your child's height?** \_\_\_\_\_

**8. What is your child's body weight?** \_\_\_\_\_



- |  |   |                                     |                   |
|--|---|-------------------------------------|-------------------|
| e. Sit unsupported?  | YES                                       | NO                                  | DON'T KNOW        |
| f. Walk with support?  | YES                                       | NO                                  | DON'T KNOW        |
| g. Walk unsupported?   | YES                                       | NO                                  | DON'T KNOW        |
| h. Feed herself using fingers?   | YES                                       | NO                                  | DON'T KNOW        |
| i. Feed herself using a spoon or fork?   | YES                                       | NO                                  | DON'T KNOW        |
| j. Communicate with gestures or sounds?  | YES                                       | NO                                  | DON'T KNOW        |
| k. Speak (words)?  | YES                                       | NO                                  | DON'T KNOW        |
| l. Make choices?   | YES                                       | NO                                  | DON'T KNOW        |
| <b>12.</b> Does your child present repetitive hand movement such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing movements? | YES                                       | NO                                  | DON'T KNOW        |
| <b>13.</b> Does your child grind her teeth repetitively?   | YES                                       | NO                                  | DON'T KNOW        |
| <b>14.</b> Is any time when your child holds her breath?   | YES                                       | NO                                  | DON'T KNOW        |
| <b>15.</b> Is there any time when your child breathing is deep and fast?   | YES                                       | NO                                  | DON'T KNOW        |
| <b>16.</b> Would you say that your child's breathing problem(s) are:   |   |                                     |                   |
| a. Minimal? <input type="checkbox"/>   | b. Intermittent? <input type="checkbox"/> | Constant? <input type="checkbox"/>  | (please tick one) |
| <b>17.</b> Are there any times when your child's abdomen feels hard?   | YES                                       | NO                                  | DON'T KNOW        |
| <b>18.</b> Does your child wake often during the night?  | YES                                       | NO                                  | DON'T KNOW        |
| <b>19.</b> Does she sleep for long periods during the day?   | YES                                       | NO                                  | DON'T KNOW        |
| <b>20.</b> Does your child self-injure?  |   |                                     |                   |
| a. No <input type="checkbox"/>   | b. Sometimes <input type="checkbox"/>     | Frequently <input type="checkbox"/> | (please tick one) |
| <b>21.</b> Does your child have weak muscle tone?  | YES                                       | NO                                  | DON'T KNOW        |
| <b>22.</b> Does your child have small feet?  | YES                                       | NO                                  | DON'T KNOW        |

23. Does your child often have cold feet?      YES    NO    DON'T KNOW

24. Does your child have small hands?      YES    NO    DON'T KNOW

25. Does your child have curvature of the spine (scoliosis)?

a. None     b. Minimal     c. Moderate     d. Severe

(please tick one)

26. Does your child have epilepsy?      YES    NO    DON'T KNOW

27. If yes at what age did the seizure start?

---

28. How many types of fit does your child have?

---

29. How often does your child have seizures?

a. None for over a year     b. Less than 1 a month

c. At least 1 per month     d. At least 1 per week

e. Daily       (please tick one)

30. Is your child currently on medication      YES    NO    DON'T KNOW  
for seizures?

31. Does your child have odd episodes where  
she appear to go blank?      YES    NO

32. Do you feel these are:

a. Associated with abnormal breathing

b. Associated with pain

c. Possibly seizures

d. Don't know

***Please check your answers and go on to the next questionnaire.***

## HEALTH QUESTIONNAIRE PART A

**Instructions:**

**Have these problems EVER affected your child with Rett Syndrome?**

**Please rate 0 – if the problem has never affected your child, 1 – if it has been a mild problem, 2 – if it has been a moderately serious problem, 3 – if it has been a severe problem.**

**Where your child has had any of these problems, please state whether there has been any treatment for them – by circling yes or no**

	Never	Mild	Moderate	Severe
1a. Eye Problems (e.g. glaucoma / blocked tear duct/s)	0	1	2	3
1b. Corrective surgery / medication / treatment:		Yes	No	
2a. Ear Problems (e.g. infections, glue ear)	0	1	2	3
2b. Corrective surgery / medication / treatment (e.g. grommets)		Yes	No	
3a. Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed eruption of teeth)	0	1	2	3
3b. Dental surgery / treatment (e.g. teeth removal)		Yes	No	
4a. Cleft Palate	0	1	2	3
4b. Repaired		Yes	No	
5a. Gastrointestinal Difficulties (e.g. reflux / stomach problems)	0	1	2	3
5b. Corrective surgery / medication / treatment		Yes	No	
6a. Bowel Problems (e.g. obstruction)	0	1	2	3
6b. Corrective surgery / treatment		Yes	No	
7a. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur)	0	1	2	3
7b. Corrective surgery / medication / treatment		Yes	No	
8a. Hernia (e.g. inguinal or hiatal)	0	1	2	3
8b. Repair / treatment		Yes	No	
9. Limb Abnormalities (e.g. malformed arm)	0	1	2	3

10a. Epilepsy / Seizures / Neurological Referrals	0	1	2	3
10b. Medication		Yes	No	
11a. Lung or Respiratory Problems (asthma/bronchitis)	0	1	2	3
11b. Corrective surgery / medication / treatment:		Yes	No	
12a. Liver or Kidney Problems	0	1	2	3
12b. Corrective surgery / medication / treatment		Yes	No	
13a. Diabetes or Thyroid Function Problems	0	1	2	3
13b. Corrective surgery / medication / treatment		Yes	No	
14a. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin)	0	1	2	3
14b. Medication / treatment		Yes	No	
15a. Other				
Please specify problem:	0	1	2	3
15b. Corrective surgery / medication / treatment		Yes	No	

## PART B

### **Instructions:**

**Have these medical problems affected the your child with Rett Syndrome in the past MONTH**

**Please rate as 0 – if your child has not been affected by this problem in the past month, 1 - if they have been mildly affected, 2 – if the problem has moderately affected your child, and 3 - if your child has been severely affected by the problem.**

	No	Mild	Moderate	Severe
17. Eye Problems (e.g. glaucoma /blocked tear duct/s)	0	1	2	3
18. Ear Problems (e.g. infections, glue ear)	0	1	2	3
19. Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed eruption of teeth)	0	1	2	3

	No	Mild	Moderate	Severe
20. Cleft Palate	0	1	2	3
21. Gastrointestinal Difficulties (e.g. reflux / stomach problems)	0	1	2	3
22. Bowel Problems (e.g. obstruction)	0	1	2	3
23. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur)	0	1	2	3
24. Hernia (e.g. inguinal or hiatal)	0	1	2	3
25. Limb Abnormalities (e.g. malformed arm)	0	1	2	3
26. Epilepsy / Seizures / Neurological Referrals	0	1	2	3
27. Lung or Respiratory Problems (asthma / bronchitis)	0	1	2	3
28. Liver or Kidney Problems	0	1	2	3
29. Diabetes or Thyroid Function Problems	0	1	2	3
30. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin)	0	1	2	3
31. Other Please specify problem:	0	1	2	3

*Please check your answers and go on to the next questionnaire.*

**ACTIVITY QUESTIONNAIRE** © Burbidge and C Oliver (2003)

**Instructions:**

**Please read each item carefully and circle the appropriate number on the scale for your child.**

**Please ensure that you indicate a response for every item. If the particular behaviour does not apply (for example, if the person is not verbal or not mobile), please circle 0 on the scale.**

		Never/ Almost never	Some of the time	Half of the time	A lot of the time	Always/ almost all the time
1.	Does your child wriggle or squirm about when seated or laying down	0	1	2	3	4
2.	Does your child fidget or play with their hands and/or feet when seated or laying down?	0	1	2	3	4
3.	Does your child find difficult holding still?	0	1	2	3	4
4.	Does your child find it difficult to remain in her seat even in situations where it would be expected?	0	1	2	3	4
5.	Does your child prefer to be moving around or become frustrated if left in one position for too long?	0	1	2	3	4
6.	When your child is involved in a leisure activity (e.g. watching TV, playing game etc.) do they make a lot of noise?	0	1	2	3	4
7.	When your child is involved in an activity, are they boisterous and/or rough?	0	1	2	3	4
8.	Does your child act as if they are “driven by a motor” (i.e. often very active)?	0	1	2	3	4
9.	Does she seem like she needs very little rest to recharge her battery?	0	1	2	3	4
10.	Does your child often talk excessively?	0	1	2	3	4
11.	Does your child’s behaviour seem difficult to manage/contain whilst out and about (e.g. in town, in supermarkets etc)?	0	1	2	3	4
12.	Do you feel that you need to keep an eye on your child at all times?	0	1	2	3	4
13.	Does your child you care for seem to act/do things without stopping to think first?	0	1	2	3	4
14.	Does your child blurt out answers before questions have been completed?	0	1	2	3	4

		<b>Never/ almost never</b>	<b>Some of the time</b>	<b>Half of the time</b>	<b>A lot of the time</b>	<b>Always/ almost all the time</b>
15.	Does your child start to respond to instructions before they have been fully given or without seeming to understand them?	0	1	2	3	4
16.	Does your child want things immediately	0	1	2	3	4
17.	Does your child find difficult to wait?	0	1	2	3	4
18.	Does your child disturb others because they have difficulty waiting for things or waiting their turn?	0	1	2	3	4

***Please check your answers and go on to the next questionnaire.***

## MOOD, INTEREST AND PLEASURE QUESTIONNAIRE

This questionnaire contains 12 questions. You should complete all 12 questions. Each will ask for your opinion about particular behaviours, which you have observed in the LAST 2 WEEKS. For every question you should circle the most appropriate response e.g.

6) In the LAST TWO WEEKS, how interested did your child appear to be in her surroundings?

Interested all  
of the time

Interested  
most of the  
time

Interested  
about half of  
the time

Interested  
some of the  
time

Never  
interested

- In the last two weeks, did your child seem...

Sad all of the  
time

Sad most of  
the time

Sad about half  
of the time

Sad some of  
the time

Never sad

*Please comment if anything has happened in the last two weeks which you feel might explain sadness if it has been observed (e.g. bereavement):*

- In the last two weeks, how often did you hear positive vocalizations\* when your child was engaged in activities\*?

All of the time

Most of the  
time

About half of  
the time

Some of the  
time

Never

\*positive vocalizations: e.g. laughing, giggling, “excited sound” etc.

\*engaged in activities: i.e. when someone is actively involved in any activity such as meal time, a social interaction, a self-care task or social outing etc.

- In the last two weeks, do you think the facial expression of your child looked “flat”\*

All of the time

Most of the  
time

About half of  
the time

Some of the  
time

Never

\*flat expression: expression seems lifeless; lacks emotional expression; seems unresponsive

- **In the last two weeks, would you say your child ...**

Cried every day	Cried nearly every day	Cried 3-4 times each week	Cried once or twice each week	Cried less than once each week
-----------------	------------------------	---------------------------	-------------------------------	--------------------------------

- **In the last two weeks, how interested did your child appear to be in her surroundings?**

Interested all of the time	Interested most of the time	Interested about half of the time	Interested some of the time	Never interested
----------------------------	-----------------------------	-----------------------------------	-----------------------------	------------------

- **In the last two weeks, did your child seem to have been enjoying life...**

All of the time	Most of the time	About half of the time	Some of the time	Never
-----------------	------------------	------------------------	------------------	-------

*Please comment if there are any reasons why your child might not have been enjoying herself e.g. illness, being in pain, experiencing a loss etc.:*

- **In the last two weeks, would you say your child smiled...**

At least once every day	At least once nearly every day	3-4 times each week	Once or twice each week	Less than once each week
-------------------------	--------------------------------	---------------------	-------------------------	--------------------------

- **In the last two weeks, how uninterested did your child seem to be in her surroundings?**

Uninterested all of the time	Uninterested most of the time	Uninterested about half of the time	Uninterested some of the time	Never Uninterested
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- **In the last two weeks, when your child was engaged in activities\*, to what extent did her facial expression suggest that she was interested in the activity?**

Interested all of the time	Interested most of the time	Interested about half of the time	Interested some of the time	Never interested
----------------------------	-----------------------------	-----------------------------------	-----------------------------	------------------

\*engaged in activities: i.e. when someone is actively involved in any activity such as meal time, social interaction, self-care or social outing etc.

\*facial expression: interest might be indicated by the degree to which the person's gaze is being directed at the person/things involved in any activity.

- **In the last two weeks, would you say that your child ...**

Laughed every day	Laughed nearly every day	Laughed 3-4 times each week	Laughed once or twice each week	Laughed once each week
-------------------	--------------------------	-----------------------------	---------------------------------	------------------------

- **In the last two weeks, how often did you see gestures which appeared to demonstrate enjoyment\* when your child was engaged in activities\*?**

All of the time	Most of the time	About half of the time	Some of the time	Never
-----------------	------------------	------------------------	------------------	-------

\*gestures which appear to demonstrate enjoyment: e.g. clapping, waving hands in excitement etc.

\*engaged in activities: i.e. when someone is actively involved in any activity such as meal time, social interaction, self-care task or social outing etc.

- **In the last two weeks, did your child's vocalization\* sound distressed...**

All of the time	Most of the time	About half of the time	Some of the time	never
-----------------	------------------	------------------------	------------------	-------

\*vocalizations: any words, noises or utterances

*Please feel free to make any additional comments about the behaviour of your child over the last two weeks:*

***Please check your answers and go on to the next questionnaire***

## RETT SYNDROME BEHAVIOUR QUESTIONNAIRE

**This questionnaire asks you about some of the behaviour that your child may display during the day or night. Please read the statement and circle 0 if the statement is not true, 1 if somewhat or sometimes true, and 2 if very true.**

	Not true	Somewhat or sometimes true	Very true
1. There are times when breathing is deep and fast (hyperventilation).	0	1	2
2. Spells of screaming for no apparent reason during the day	0	1	2
3. Makes repetitive hands movements with hands apart	0	1	2
4. Makes repetitive hand movements involving fingers around tongue	0	1	2
5. There are times when breath is held	0	1	2
6. Air or saliva expelled from mouth with force	0	1	2
7. Spells of apparent anxiety/fear in unfamiliar situations.	0	1	2
8. Grinds teeth.	0	1	2
9. Seems frightened when sudden changes in body position.	0	1	2
10. There are times when parts of the body are held rigid.	0	1	2
11. Shifts gaze with slow horizontal head turn	0	1	2
12. Expressionless face	0	1	2
13. Spells of screaming for no apparent reason during the night	0	1	2
14. Abrupt changes in mood	0	1	2
15. There are certain periods when performs much worse than usual.	0	1	2
16. There are times when appears miserable for no apparent reason	0	1	2
17. Seems to look through people into the distance.	0	1	2
18. Does not use hands for purposeful grasping	0	1	2
19. Swallows air	0	1	2
20. Hands movements uniform and monotonous	0	1	2
21. Has frequent naps during the day	0	1	2
22. Screams hysterically for long periods of time and cannot be consoled	0	1	2
23. Although can stand independently tends to lean on objects or people.	0	1	2
24. Restricted repertoire of hands movement	0	1	2
25. Abdomen fills with air and sometimes feels hard	0	1	2
26. Spells of laughter for no apparent reason during the day.	0	1	2
27. Has wounds on hands as a result of repetitive hands movements.	0	1	2
28. Makes mouth grimaces	0	1	2

	<b>Not true</b>	<b>Somewhat or sometimes true</b>	<b>Very true</b>
29. There are times when irritable for no apparent reason	0	1	2
30. Spells of inconsolable crying for no apparent reason during the day	0	1	2
31. Uses eye gaze to convey feeling, needs and wishes	0	1	2
32. Makes repetitive tongue movements	0	1	2
33. Rocks self when hands are prevented from moving	0	1	2
34. Makes grimacing expressions with face	0	1	2
35. Has difficulties in breaking/stopping hand stereotypes	0	1	2
36. Vocalises for no apparent reason	0	1	2
37. Spells of laughter for no apparent reason during the night	0	1	2
38. Spells of apparent panic.	0	1	2
39. Walks with stiff legs.	0	1	2
40. Tendency to bring hands together in front of chin or chest.	0	1	2
41. Rocks body repeatedly	0	1	2
42. Spells of inconsolable crying for no apparent reason during the night	0	1	2
43. The amount of time spent looking at objects is longer than time spent holding or manipulating them.	0	1	2
44. Appears isolated	0	1	2
45. Vacant 'staring' spells	0	1	2

*Please check your answers and go on to the next questionnaire*

## CHALLENGING BEHAVIOUR QUESTIONNAIRE

- Has your child shown self-injurious behaviour IN THE LAST MONTH? (i.e. Head banging, head-punching or slapping, remove hair, self-scratching, body hitting, eye pocking or pressing)

YES  NO  (Please tick)

*If the behaviour has not occurred, please go to question 6*

*If the behaviour has occurred in the past month please answer all of the following questions:*

- Place a tick next to the item for any of the following list of behaviours which your child displays in a repetitive manner (i.e., repeats the same movement / behaviour twice or more in succession):

Hits self with body part (e.g. slap head or face)	<input type="checkbox"/>
Hits self against surface or object (bangs head on floor or table)	<input type="checkbox"/>
Hits self with object	<input type="checkbox"/>
Bites self (bites hand or wrist or harm)	<input type="checkbox"/>
Pulls hair or skin	<input type="checkbox"/>
Rubs or scratches self (e.g. rub marks on harm or leg)	<input type="checkbox"/>
Inserts finger or objects (e.g. eye pocking)	<input type="checkbox"/>
Other form of self-injury, please specify _____	<input type="checkbox"/>

- In the last month, for how long did the **longest** episode or burst of her behaviour last? *(Please circle one number)*

1	2	3	4	5
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

- In the last month as a result of her behaviour, has physical contact or prevention or restraint by others been necessary, e.g. blocking, taking objects from an individual, temporary restrain of an arm? *(Please circle one number)*

0	1	2	3	4
Never	At least once	At least once a week	At least once a day	At least an hour

- Think about how often this behaviour occurred in the last month. If there was no change and you watched your child now, then would you definitely see the behaviour? *(Please circle one number)*

1	2	3	4	5
By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

- Has your child shown physical aggression in the last month? (Punching, pushing, kicking, pulling hair, grabbing other's clothes)

YES  NO  *(Please tick)*

- Has your child shown disruption and destruction of property or the environment in the last month? (e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal)

YES  NO  *(Please tick)*

- Has your child shown stereotyped behaviour in the last month? (e.g. rocking, twiddling objects, patting or tapping part of the body, constant hand movements, eye pressing).

YES  NO  *(Please tick)*

***Please check your answers and go on to the next questionnaire***

## REPETITIVE BEHAVIOUR QUESTIONNAIRE

### Instructions:

- The questionnaire asks about 19 different behaviours.
- Each behaviour is accompanied by a brief definition and examples. The examples given for each behaviour are not necessarily a complete list but may help you to understand the definitions more fully.
- Please read the definitions and examples carefully and circle the appropriate number on the scale to indicate how frequently your child has engaged in each of the behaviours **WITHIN THE LAST MONTH**.
- If a particular behaviour does not apply to your child because they are not mobile or verbal please circle the number 0 on the scale.

	Never	Once a month	One a week	Once a day	More than once a day
· <b>Object stereotypy:</b> repetitive, seemingly purposeless movement of objects in an unusual way, e.g. <i>twirling or twiddling objects, twisting or shaking, banging or slapping objects</i>	0	1	2	3	4
· <b>Body stereotypy:</b> repetitive, seemingly purposeless movement of whole body or part of body (other than hands) in an unusual way. e.g. <i>body rocking, or swaying or spinning, bouncing, head shaking, body posturing</i> . Does not include self-injurious behaviour.	0	1	2	3	4
· <b>Hands stereotypy:</b> repetitive, seemingly purposeless movements of hands in an unusual way. e.g. <i>finger twiddling, hand flapping, wiggling or flicking fingers, hand posturing</i> . Does not include self-injurious behaviour	0	1	2	3	4
· <b>Cleaning:</b> excessive cleaning, washing or polishing of objects or part of the body. e.g. <i>polishes windows and surfaces excessively, washes hands and face excessively</i> .	0	1	2	3	4
· <b>Tiding up:</b> tiding away any objects that have been left out. This may occur in situations when it is appropriate to put the objects away. Objects may be put away into inappropriate places. e.g. <i>putting cutlery left out for dinner in the bin, removes all objects from surfaces</i>	0	1	2	3	4
· <b>Hoarding:</b> collecting, storing or hiding objects to excess, including rubbish, bits of paper, and pieces of string or any other unusual items	0	1	2	3	4
· <b>Organising objects:</b> organising objects into categories according to various characteristics such as colour, size or function. e.g. <i>ordering magazines according to size, ordering toy cars according to colour, ordering books according to topics</i> .	0	1	2	3	4
· <b>Attachment to particular people:</b> continually asking to see, speak or contact a particular 'favourite' person. e.g. <i>continually asks to see or speak to particular friend, carer, babysitter or schoolteacher</i> .	0	1	2	3	4

		Never	Once a month	One a week	Once a day	More than once a day
·	<b>Repetitive questions:</b> asking specific question over and over. e.g. <i>always asking people what their favourite colour is, asking who is taking them to school the next day over and over.</i>	0	1	2	3	4
·	<b>Attachment to objects:</b> strong preference for a particular object to be present at all times. e.g. <i>carrying a particular piece of string everywhere, attachment to soft toy or particular blanket.</i>	0	1	2	3	4
·	<b>Repetitive phrases/signing:</b> repeating particular sounds, phrases or signs that are unrelated to the situation over and over. e.g. <i>repeatedly signing the word telephone.</i>	0	1	2	3	4
·	<b>Rituals:</b> carrying out a sequence of unusual or bizarre actions before, during or after a task. The sequence will always be carried out when performing this task and will always occur in the same way. e.g. <i>turning round three times before sitting down, turning lights on and off twice before leaving a room, tapping door frame twice when passing through it.</i>	0	1	2	3	4
·	<b>Restricted conversation:</b> repeatedly talks about specifics, unusual topics in great detail. e.g. <i>conversation restricted to: train, buses, dinosaurs, particular film, country or sport.</i>	0	1	2	3	4
·	<b>Echolalia:</b> repetition of speech that has either just heard or has been heard more than a minute earlier. e.g. <i>mum: 'Jack don't do that' Jack: 'jack don't do that'</i>	0	1	2	3	4
·	<b>Preference for routine:</b> insists of having the same household, school or work schedule everyday. e.g. <i>likes to have the same activities on the same day at the same time each week, prefer to eat lunch at exactly the same time every day, wearing the same jumper everyday.</i>	0	1	2	3	4
·	<b>Lining up or arranging objects:</b> arrangement of objects into lines or patterns. e.g. <i>placing toy cars in a symmetrical pattern, precisely lining up story books.</i>	0	1	2	3	4
·	<b>Just right behaviours:</b> strong insistence that objects, furniture and toys always remain in the same place. e.g. <i>all chair, pictures and toys have a very specific place that cannot be changed.</i>	0	1	2	3	4
·	<b>Completing behaviour:</b> insists on having objects or activities 'complete' or 'whole'. e.g. <i>must have doors open or closed not in between, story must be read from beginning to end, no left half way through.</i>	0	1	2	3	4
·	<b>Spotless behaviour:</b> removing small, almost unnoticeable piece of lint, fluff, crumbs or dirt from surfaces, clothes and objects. e.g. <i>picking fluff or jumper, removing crumbs from the kitchen table.</i>	0	1	2	3	4

*Please check your answers and go on to the next questionnaire*

## DEVELOPMENTAL BEHAVIOUR CHECKLIST

**Some children with developmental delay have problems with their emotions and behaviour. These can sometimes be a problem for their carers.**

**By completing this checklist, you will help us learn more about these problems.**

### Instructions:

**Many of the following behaviours may not apply to your child with Rett Syndrome. For each that does describe your child with Rett Syndrome, now or within the past six months, please circle:**

**0 = not true; 1 = sometimes or somewhat true; 2 = very true or often true.**

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Appears depressed, downcast or unhappy.	0	1	2
Avoids eye contact, won't look you straight in the eye	0	1	2
Aloof, in her own world.	0	1	2
Abusive. Swear at others.	0	1	2
Arranges objects or routine in a strict order. Please describe: _____	0	1	2
Bangs head.	0	1	2
Becomes over-excited.	0	1	2
Bites others.	0	1	2
Cannot attend to one activity for any length of time, poor attention span.	0	1	2
Chews or mouths objects, or body part.	0	1	2
Cries easily for no reason, or over small upsets.	0	1	2
Covers ears or is distressed when hears particular sounds. Please describe: _____	0	1	2
Confuses the use of pronouns e.g. uses "you" instead of "I".	0	1	2
Deliberately runs away.	0	1	2
Delusions: has a firmly held belief or idea that can't possibly be true. Please describe: _____	0	1	2
Distressed about being alone.	0	1	2
Doesn't show affection.	0	1	2

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Doesn't respond to others' feelings, e.g. shows no response if familiar member is crying.	0	1	2
Easily distracted from her task, e.g. by noise.	0	1	2
Easily led by others.	0	1	2
Eats non-food items e.g. dirt, grass, soap.	0	1	2
Excessively distressed if separated from familiar person.	0	1	2
Fears particular things or situations, e.g. the dark or insects.	0	1	2
Please describe: _____			
Facial twitches or grimaces.	0	1	2
Flicks, taps, twirls objects repeatedly.	0	1	2
Fussy food eater or has food fads.	0	1	2
Gorges food. Will do anything to get food, e.g. takes food out of garbage bins or steals food.	0	1	2
Gets obsessed with an idea or activity. Please describe: _____	0	1	2
Grinds teeth.	0	1	2
Has nightmares, night terrors or walks in sleep.	0	1	2
Has temper tantrums, e.g. stamps feet, slams doors.	0	1	2
Hides things.	0	1	2
Hits self or bites self.	0	1	2
Hums, whines, grunts, squeals or makes other non speech noises.	0	1	2
Impatient.	0	1	2
Inappropriate sexual activity with another.	0	1	2
Impulsive, acts before thinking.	0	1	2
Irritable.	0	1	2
Jealous.	0	1	2
Kicks, hits other.	0	1	2
Lacks self-confidence, poor self esteem.	0	1	2
Laughs or giggles for no obvious reason.	0	1	2
Lights fires.	0	1	2

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Likes to hold or play with an unusual object, e.g. string, twigs; overly fascinated with something, e.g. water. Please describe: _____	0	1	2
Loss of appetite.	0	1	2
Masturbates or exposes self in public.	0	1	2
Mood changes rapidly for no apparent reason.	0	1	2
Moves slowly, under active, does little, e.g. only sits and watches others.	0	1	2
Noisy or boisterous.	0	1	2
Overactive, restless, unable to sit still.	0	1	2
Over affectionate.	0	1	2
Over breathes, vomits, has headaches or complains of being sick for no physical reason.	0	1	2
Overly attention-seeking.	0	1	2
Overly interested in looking at, listening to or dismantling mechanical things, e.g. lawnmower, vacuum cleaner.	0	1	2
Poor sense of danger.	0	1	2
Prefers the company of adults or younger children; doesn't mix with her own age group.	0	1	2
Prefers to do things on her own. Tends to be a loner.	0	1	2
Preoccupied with only one or two particular interests. Please describe: _____	0	1	2
Refuses to go school, activity centre or workplace.	0	1	2
Repeated movements of hands, body, head or face e.g. hand flapping or rocking.	0	1	2
Resists being cuddled, touched or held.	0	1	2
Repeats back what others say like an echo.	0	1	2
Repeats the same word or phrases over and over.	0	1	2
Smells, tastes or licks objects.	0	1	2
Scratches or picks her skin.	0	1	2
Screams a lot.	0	1	2

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Sleeps too little. Disrupted sleep.	0	1	2
Stares at lights or spinning objects	0	1	2
Sleeps too much.	0	1	2
Soils outside toilet though toilet trained. Smears or plays with faeces.	0	1	2
Speaks in whispers, high pitches voice, or other unusual tone or rhythm.	0	1	2
Switches lights on and off, pour water over and over; or similar repetitive activity. Please describe: _____	0	1	2
Steals.	0	1	2
Stubborn, disobedient or uncooperative.	0	1	2
Shy.	0	1	2
Strips clothes or throws away clothes.	0	1	2
Says she can do things that she is not capable of.	0	1	2
Stands too close to others.	0	1	2
Sees, hears, something which isn't there. Hallucinations. Please describe: _____	0	1	2
Talks about suicide.	0	1	2
Talks too much or too fast.	0	1	2
Talks to self or imaginary people or objects.	0	1	2
Tells lie.	0	1	2
Thoughts are unconnected. Different ideas are jumbled together with meaning difficult to follow.	0	1	2
Tense, anxious, worried.	0	1	2
Throws or breaks objects.	0	1	2
Tries to manipulate or provoke others.	0	1	2
Under reacts to pain.	0	1	2
Unrealistically unhappy or elated.	0	1	2
Unusual body movements, posture, or way of walking. Please describe: _____	0	1	2

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Upset and distressed over small changes in routine or environment. Please describe: _____	0	1	2
Urinating outside toilet, although toilet trained.	0	1	2
Very bossy.	0	1	2
Wanders aimlessly.	0	1	2
Whines or complains a lot	0	1	2
Please write in any problems your child has that were not listed above _____	0	1	2
_____	0	1	2
_____	0	1	2
Overall, do you feel your child has problems with feelings or behaviour, in addition to problems with development? If not, please circle the 0. If so, but they were minor, please circle 1. If they were major problems, please circle 2.	0	1	2

*Thank you for completing part 1 of the questionnaire pack.*

*Please check your answers and go on to part 2 of the questionnaire.*

**Developmental Behavior Checklist Adult Version**

## DEVELOPMENTAL BEHAVIOUR CHECKLIST

Some people with developmental delay have problems with their emotions and behaviour. These can sometimes be a problem for their carers.  
By completing this checklist, you will help us learn more about these problems.

**Instructions:**  
**Many of the following behaviours may not apply to your daughter with Rett Syndrome. For each that does describe your daughter with Rett Syndrome, now or within the past six months, please circle:**  
**0 = not true; 1 = sometimes or somewhat true; 2 = very true or often true.**

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Appears depressed, downcast or unhappy.	0	1	2
Avoids eye contact, won't look you straight in the eye	0	1	2
Aloof, in her own world.	0	1	2
Abusive. Swear at others.	0	1	2
Arranges objects or routine in a strict order. Please describe: _____	0	1	2
Bangs head.	0	1	2
Becomes over-excited.	0	1	2
Bites others.	0	1	2
Bizarre speech. Please describe: _____	0	1	2
Cannot attend to one activity for any length of time, poor attention span.	0	1	2
Chews or mouths objects, or body part.	0	1	2
Cries easily for no reason, or over small upsets.	0	1	2
Covers ears or is distressed when hears particular sounds. Please describe: _____	0	1	2
Confuses the use of pronouns e.g. uses "you" instead of "I".	0	1	2
Deliberately runs away.	0	1	2
Delusions: has a firmly held belief or idea that can't possibly be true. Please describe _____	0	1	2

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Distressed about being alone.	0	1	2
Doesn't show affection.	0	1	2
Doesn't respond to others' feelings, e.g. shows no response if familiar member is crying.	0	1	2
Easily distracted from her task, e.g. by noise	0	1	2
Easily led into trouble by others.	0	1	2
Eats non-food items e.g. dirt, grass, soap.	0	1	2
Excessively distressed if separated from familiar person.	0	1	2
Fears particular things or situations, e.g. the dark, insects or crowds.	0	1	2
Please describe: _____			
Facial twitches or grimaces.	0	1	2
Flicks, taps, twirls objects repeatedly.	0	1	2
Fussy eater or has food fads.	0	1	2
Gorges food. Will do anything to get food, e.g. takes food out of garbage bins or steals food.	0	1	2
Gets obsessed with an idea or activity. Please describe: _____	0	1	2
Grinds teeth.	0	1	2
Has becomes confused or forgetful.	0	1	2
Has becomes more withdrawn.	0	1	2
Has nightmares, night terrors or walks in sleep.	0	1	2
Has temper tantrums, e.g. stamps feet, slams doors.	0	1	2
Hides things.	0	1	2
Hits self or bites self.	0	1	2
Hums, whines, grunts, squeals or makes other non speech noises.	0	1	2
Impatient.	0	1	2
Inappropriate sexual activity with another.	0	1	2
Increase in appetite.	0	1	2
Impulsive, acts before thinking.	0	1	2

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Irritable.	0	1	2
Jealous.	0	1	2
Kicks, hits or injures other.	0	1	2
Lacks self-confidence, poor self esteem.	0	1	2
Laughs or giggles for no obvious reason.	0	1	2
Lights fires.	0	1	2
Likes to hold or play with an unusual object, e.g. string, twigs; overly fascinated with something, e.g. water. Please describe: _____	0	1	2
Loss of appetite.	0	1	2
Loss of enjoyment or interest in usual activities.	0	1	2
Loss of self-care skills.	0	1	2
Makes gloomy statements.	0	1	2
Masturbates or exposes self in public.	0	1	2
Mood changes rapidly for no apparent reason.	0	1	2
Moves slowly, under active, does little, e.g. only sits and watches others.	0	1	2
Noisy or boisterous.	0	1	2
Not communicating as much as usual.	0	1	2
Overactive, restless, unable to sit still.	0	1	2
Over affectionate.	0	1	2
Over breathes, vomits, has headaches or complains of being sick for no physical reason.	0	1	2
Overly attention-seeking.	0	1	2
Overly interested in looking at, listening to or dismantling mechanical things, e.g. lawnmower, vacuum cleaner.	0	1	2
Panics, sweats, flushes, trembles.	0	1	2
Poor sense of danger.	0	1	2
Prefers to do things on her own. Tends to be a loner.	0	1	2
Preoccupied with only one or two particular interests. Please describe: _____	0	1	2

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Problems with cigarettes, alcohol or caffeine.	0	1	2
Problems with the legal use of drugs.	0	1	2
Refuses to go college, activity centre or workplace.	0	1	2
Repeated movements of hands, body, head or face e.g. hand flapping or rocking.	0	1	2
Resists being cuddled, touched or held.	0	1	2
Repeats back what others say like an echo.	0	1	2
Repeats the same word or phrases over and over.	0	1	2
Smells, tastes or licks objects.	0	1	2
Scratches or picks her skin.	0	1	2
Screams a lot.	0	1	2
Sleeps too little. Disrupted sleep.	0	1	2
Stares at lights or spinning objects.	0	1	2
Sleeps too much or overly drowsy.	0	1	2
Soils outside toilet though toilet trained; smears or plays with faeces.	0	1	2
Speaks in whispers, high pitches voice, or other unusual tone or rhythm.	0	1	2
Spits.	0	1	2
Switches lights on and off, pour water over and over; or similar repetitive activity. Please describe: _____	0	1	2
Steals.	0	1	2
Stubborn, disobedient or uncooperative.			
Shy.	0	1	2
Strips clothes or throws away clothes.	0	1	2
Says she can do things that she is not capable of.	0	1	2
Stands too close to others.	0	1	2
Sees, hears, something which isn't there. Hallucinations. Please describe: _____	0	1	2
Talks about or attempt suicide.	0	1	2
Talks too much or too fast.	0	1	2

	Not true as far as I know	Sometimes or somewhat true	Often true or very true
Talks to self or imaginary people or objects.	0	1	2
Tells lie.	0	1	2
Thoughts are unconnected. Different ideas are jumbled together with meaning difficult to follow	0	1	2
Tense, anxious, worried.	0	1	2
Throws or breaks objects.	0	1	2
Tries to manipulate or provoke others.	0	1	2
Under reacts to pain.	0	1	2
Unrealistically unhappy or elated.	0	1	2
Unusual body movements, posture, or way of walking. Please describe:_____	0	1	2
Upset and distressed over small changes in routine or environment. Please describe:_____	0	1	2
Urinating outside toilet, although toilet trained.	0	1	2
Very bossy.	0	1	2
Wanders aimlessly.	0	1	2
Whines or complains a lot.	0	1	2
Please write in any problems your daughter has that were not listed above_____	0	1	2
_____	0	1	2
_____	0	1	2
Overall, do you feel your daughter has problems with feelings or behaviour, in addition to problems with development? If not, please circle the 0. If so, but they were minor, please circle 1. If they were major problems, please circle 2.	0	1	2

***Thank you for completing part 1 of the questionnaire pack.  
Please check your answers and go on to part 2 of the questionnaire.***



## **Support needs of Girls/Women with Rett Syndrome and their Families**

### **PART 2: FAMILY NEEDS AND RETT SYNDROME**

- This section of the questionnaire will ask you questions about you and your family. We would like you to tell us about your experience of having a child with Rett Syndrome and what can be done to improve the support you receive.
15. The questionnaires should be completed by the main caregiver. You do not have to complete them all in one go. Please find time when it is convenient to you.
- When you have completed all the questionnaires, please check that you have answered every question in each questionnaire, and return the pack to me in the pre-paid envelope provided.
  - In the pack we have included a checklist of the separate questionnaires that I have sent you. Please use this to make sure that you are returning all of the questionnaires.

***Thank you for agreeing to participate in this research and for taking the time to complete the questionnaires.***

Rina Cianfaglione  
PhD Student

Welsh Centre for Learning Disabilities, School of Medicine, Cardiff University

## CHECKLIST OF QUESTIONNAIRES

### PART 2 YOU AND YOUR FAMILY

THIS SECTION OF THE QUESTIONNAIRE ASKS QUESTIONS ABOUT YOU AND YOUR FAMILY. PLEASE GIVE THE ANSWER THAT DESCRIBES YOUR FEELING MOST ACCURATELY.

**PLEASE READ THE INSTRUCTIONS CAREFULLY AND COMPLETE THE FOLLOWING QUESTIONNAIRES**

**PLEASE COMPLETE THE QUESTIONNAIRES AT A TIME CONVENIENT TO YOU. YOU DO NOT HAVE TO COMPLETE THEM ALL IN ONE GO**

- BACKGROUND INFORMATION \_\_\_\_\_
- PARENTING AND THE FAMILY \_\_\_\_\_
- RAISING A CHILD WITH RETT SYNDROME \_\_\_\_\_
- YOUR DAY TO DAY FEELINGS \_\_\_\_\_
- YOUR FEELINGS AND EMOTIONS \_\_\_\_\_
- SUPPORT FOR YOUR FAMILY \_\_\_\_\_
- SOURCES OF STRESS \_\_\_\_\_
- PARENTAL PERCEPTION OF REGRESSION/PROGRESSION OF SKILLS \_\_\_\_\_
- SIBLINGS \_\_\_\_\_

## BACKGROUND INFORMATION

**The following questions ask for information about you and your family.  
Please tick the appropriate boxes or write in the spaces provided.**

- **Are you male or female?**    Male     Female
- **What was your age in years on your last birthday?** \_\_\_\_\_
- **Please tick the highest level of your educational qualifications**
  - a. No formal education qualifications.....
  - b. Fewer than 5 GSSE' or O Level's (grades A-C), NVQ1, or BTEC First Diploma.....
  - c. 5 or more GCSE' or O Level 's (grades A-C), NVQ 2, or equivalent.....
  - d. 3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent.....
  - e. Polytechnic/University degree, NVQ 4, or equivalent.....
  - f. Master/Doctoral degree, NVQ 5, or equivalent.....
- **In total how many people currently live in your home?** \_\_\_\_\_ **Adults** \_\_\_\_\_ **Children**
- **Does your daughter with Rett Syndrome live with you?**    Yes     No   
**If no, then where does she live?** \_\_\_\_\_
- **What is your current marital status?**
  - a. Married, and living with spouse.....
  - b. Living with partner.....
  - c. Divorced/Separated/Widowed/Single and not living with partner.....

**If living with partner/spouse, please answer the following questions, if not, please go to question 12.**

- **Is your partner male or female?**    Male     Female
- **What was their age in years on their last birthday?** \_\_\_\_\_ years
- **Please tick the highest level of your partner/spouse's educational qualifications.**
  - a. No formal education qualifications.....
  - b. Fewer than 5 GSSE' or O Level's (grades A-C), NVQ1, or BTEC First Diploma.....
  - c. 5 or more GCSE' or O Level 's (grades A-C), NVQ 2, or equivalent.....
  - d. 3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent.....

e. Polytechnic/University degree, NVQ 4, or equivalent.....

f. Master/Doctoral degree, NVQ 5, or equivalent.....

- **What is your partner/spouse's relationship to your child with Rett Syndrome (e.g., mother, father, stepmother, adoptive parent)?**

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*Please check your answer and go on to the next questionnaire*

## PARENTING AND THE FAMILY

The following statements deal with your feelings about your child with Rett Syndrome. There are many blank spaces on the questionnaire (\_\_\_\_\_). Imagine the name of your child with Rett Syndrome in each of these blank spaces. Please give your honest feelings and opinions. Respond to all of the statements even if they do not seem to apply. If it is difficult to decide “true” or “false” answer in terms of what you or your family feel or do *most* of the time. Sometimes the statements will refer to difficulties that are not applicable to your family. These statements can still be responded to with a “true” or “false”.  
Please respond to all of the statements by circling either TRUE or FALSE.

Other members of the family have to do without things because of _____	TRUE	FALSE
Our family agrees on important matters.	TRUE	FALSE
The constant demands for care for _____ limit growth and development of someone else in our family.	TRUE	FALSE
I have given up things I have really wanted to do in order to care for _____	TRUE	FALSE
_____ is able to fit into the family social group.	TRUE	FALSE
In the future, our family’s social life will suffer because of increased responsibilities and financial stress.	TRUE	FALSE
I can go to visit friends whenever I want.	TRUE	FALSE
Taking _____ on a holiday spoils the pleasure for the whole family.	TRUE	FALSE
The family does as many things together now as we ever did.	TRUE	FALSE
There are many places where we can enjoy ourselves as a family when _____ comes along.	TRUE	FALSE
I get almost too tired to enjoy myself.	TRUE	FALSE
There is a lot of anger and resentment in our family.	TRUE	FALSE
The constant demands to care for _____ limit my growth and development.	TRUE	FALSE
I feel sad when I think of _____.	TRUE	FALSE
Caring for _____ puts a strain on me.	TRUE	FALSE
Members of our family get to do the same kinds of things other families do.	TRUE	FALSE

*Please check your answer and go on to the next questionnaire*

## RAISING A CHILD WITH RETT SYNDROME

**The following questions ask about your feelings associated with raising a child with Rett Syndrome. Please circle the answer that comes closest to describing how you feel. Your first reaction to each question should be your answer.**

	Strongly Agree	Agree	Not sure	Disagree	Strongly Disagree
1. Since having this child I feel I have grown as a person.	SA	A	NS	D	SD
2. Having this child has helped me to learn new things/skills.	SA	A	NS	D	SD
3. Raising this child helps putting life into perspective.	SA	A	NS	D	SD
4. Since having this child, my family has become closer to one another.	SA	A	NS	D	SD
5. Since having this child my family has become more tolerant and accepting	SA	A	NS	D	SD
6. Since having this child I have become more determined to face up to challenges.	SA	A	NS	D	SD
7. Since having this child I have a greater understanding of other people.	SA	A	NS	D	SD

*Please check your answer and go on to the next questionnaire*

## YOUR DAY TO DAY FEELINGS

The following questions focus on how *you* feel about things. Please read each item and circle the reply underneath the item which comes closest to how you have been feeling in the past week. Do not take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

**1. I feel tense or “wound up”**

Most of the  
time

A lot of the  
time

Occasionally/from  
time to time

Not at all

**2. I still enjoy the things I used to enjoy**

Definitely as  
much

Not quite so  
much

Only a little

Hardly at all

**3. I get a sort of frightened feeling as if something awful is about to happen**

Very definitely and  
quite badly

Yes, but not  
too badly

A little, but it  
doesn't worry me

Not at all

**4. I can laugh and see the funny side of things**

As much as I  
always could

Not quite so  
much now

Definitely not  
so much now

Not at all

**5. Worrying thoughts go through my mind**

A great deal of  
the time

A lot of the  
time

From time to time  
but not too often

Only  
occasionally

**6. I feel cheerful**

Not at all

Not often

Sometimes

Most of the time

**7. I can sit at ease and feel relaxed**

Definitely

Usually

Not often

Not at all

**8. I feel as if I am slowed down**

Nearly all the  
time

Very often

Sometimes

Not at all

**9. I get a sort of frightened feeling like “butterflies” in the stomach**

Not at all

Occasionally

Quite often

Very often

**10. I have lost interest in my appearance**

Definitely	I don't take as much care as I should	I may not take quite as much care	I take just as much care as ever
------------	---------------------------------------	-----------------------------------	----------------------------------

**11. I feel restless as if I have to be on the move**

Very much indeed	Quite a lot	Not very much	Not at all
------------------	-------------	---------------	------------

**12. I look forward with enjoyment to things**

As much as I ever did	Rather less than I used to	Definitely less than I used to	Hardly at all
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**13. I get sudden feelings of panic**

Very often indeed	Quite often	Not very often	Not at all
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**14. I can enjoy a good book, radio or TV program**

Often	Sometimes	Not often	Very seldom
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*Please check your answer and go on to the next questionnaire*

**YOUR FEELINGS AND EMOTIONS**

**This scale consists of a number of words that describe different feelings and emotions. Read each item and then circle one of the responses indicating to what extent you have felt this in the past week.**

	<i>Very slight/ not at all</i>	<i>A little</i>	<i>Moderate</i>	<i>Quite a bit</i>	<i>Extremely</i>
1. Interested	1	2	3	4	5
2. Excited	1	2	3	4	5
3. Strong	1	2	3	4	5
4. Enthusiastic	1	2	3	4	5
5. Proud	1	2	3	4	5
6. Alert	1	2	3	4	5
7. Inspired	1	2	3	4	5
8. Determined	1	2	3	4	5
9. Attentive	1	2	3	4	5
10. Active	1	2	3	4	5

*Please check your answer and go on to the next questionnaire*

YOUR VIEWS ABOUT YOURSELF

**The next questions are about how you feel about yourself. Please rate how much you agree or disagree with each of the following statements. Circle one number.**

	<i>Strongly Agree</i>	<i>Agree</i>	<i>Disagree</i>	<i>Strongly Disagree</i>
1. On the whole, I am satisfied with myself.	1	2	3	4
2. At times I think I am no good at all.	1	2	3	4
3. I am able to do things as well as most other people.	1	2	3	4
4. I certainly feel useless at times	1	2	3	4
5. All in all, I am inclined to feel that I am a failure.	1	2	3	4
6. I take a positive attitude toward myself.	1	2	3	4

*Please check your answer and go on to the next questionnaire*

## PARENTAL PERCEPTION OF PROGRESS

This questionnaire asks you questions about your perception of the progress your child with Rett Syndrome has made in the last 3 years. Please tick the response that is most appropriate. You can also add a short comment if you think it would be useful.

It would be very useful if you could add comments where possible.

Since the initial regression typical of Rett Syndrome, do you think over the past 3 years that your daughter has made progress in the following areas:

**1. BREATHING DIFFICULTIES** (breath holding, breathing fast and deep, air swallowing, expulsion of saliva)

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**2. PHYSICAL FITNESS / ROBUSTNESS**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**3. MOBILITY / WALKING**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**4. COMMUNICATION**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**5. PURPOSEFUL HAND USE**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**6. REPETITIVE HAND MOVEMENTS**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**7. BODY ROCKING**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**8. MOOD CHANGES/UNHAPPY FOR UNKNOWN REASON**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**9. PROBLEMS WITH ANXIETY**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**10. NIGHT TIME BEHAVIOURS**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**11. FEEDING PROBLEMS AND NUTRITION**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

**12. OTHER HEALTH PROBLEMS**

- a. Getting better.....
- b. Staying the same.....
- c. Getting worse.....

*Please check your answers and go on to the next questionnaire*

**THIS SECTION OF THE QUESTIONNAIRE ASKS QUESTIONS ABOUT SIBLINGS. IF YOUR CHILD WITH RETT SYNDROME IS AN ONLY CHILD YOU DO NOT NEED TO COMPLETE THIS SECTION.**

**SIBLINGS**

If there are other children living in the house how are they related to your child with **Rett Syndrome** (e.g. biological brother, step brother)? – *Please list ALL children*

**Child 1. Sex:.....Age:.....Relationship to child.....**

**Any special needs?**

**If yes, please state.....**

**Child 2. Sex:.....Age:.....Relationship to child.....**

**Any special needs?**

**If yes, please state.....**

**Child 3. Sex:.....Age:.....Relationship to child.....**

**Any special needs?**

**If yes, please state.....**

**Child 4. Sex:.....Age:.....Relationship to child.....**

**Any special needs?**

**If yes, please state.....**

**Child 5. Sex:.....Age:.....Relationship to child.....**

**Any special needs?**

**If yes, please state.....**

*Please check your answers and go on to the next questionnaire*

## RESOURCES

Recent data from research with families of children with special needs has shown that a family's financial resources are important in understanding family member's views and experiences. With this in mind, we would be very grateful if you could answer the additional question below. We are not interested in exactly what your family income is, but we would like to be able to look at whether those with high versus lower levels of financial resources have different experiences.

**What is your current total annual family income? Please include a rough estimate of total salaries and other income (including benefits) before tax and national insurance/pensions?**

**Please tick one box only:**

- |                         |                          |
|-------------------------|--------------------------|
| Less than £15,000.....  | <input type="checkbox"/> |
| £15,001 to £25,000..... | <input type="checkbox"/> |
| £25,001 to £35,000..... | <input type="checkbox"/> |
| £35,001 to £45,000..... | <input type="checkbox"/> |
| £45,001 to £55,000..... | <input type="checkbox"/> |
| £55,000 to £65,000..... | <input type="checkbox"/> |
| £65,001 or more.....    | <input type="checkbox"/> |

**THANK YOU FOR TAKING THE TIME TO COMPLETE THIS  
QUESTIONNAIRE**

**APPENDIX D**  
**NORMALITY TESTS**

## Appendix D – 1: Severity score normality test

Table D – 1.1: Severity score tests of normality

	Kolmogorov-Smirnov (df)	Asimp.Sig. (2 tail)	Shapiro-wilk	Asimp.Sig. (2 tail)
Total severity score	.116 (91)	.004	.960 (91)	.007
Sitting domain	.361 (91)	.000	.693 (91)	.000
Walking domain	.277 (91)	.000	.819 (91)	.000
Hand use	.337 (91)	.000	.735 (91)	.000
Speech Domain	.319 (91)	.000	.774 (91)	.000
Epilepsy Domain	.428 (91)	.000	.593 (91)	.000
Scoliosis domain	.282 (91)	.000	.828 (91)	.000

Figure D – 1.1: Baseline Severity score Total hystogram

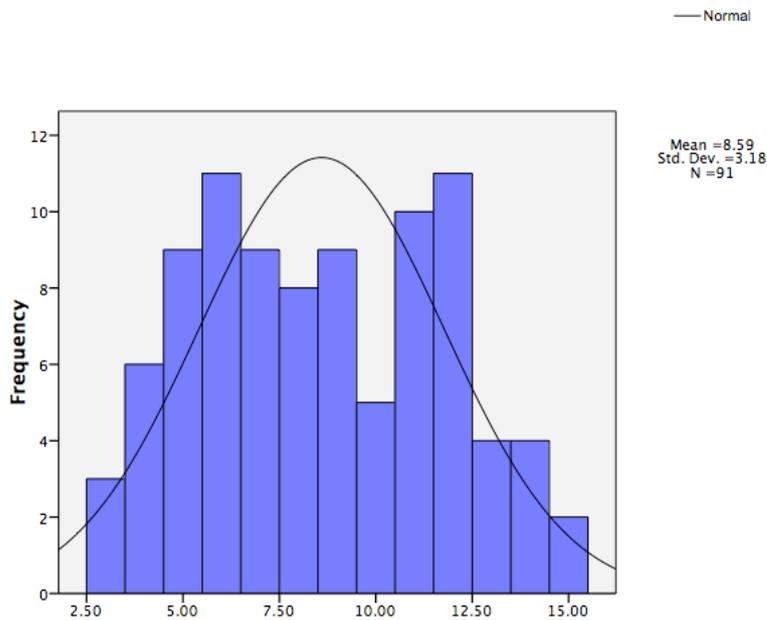


Figure D – 1.2: Baseline Sitting domain histogram

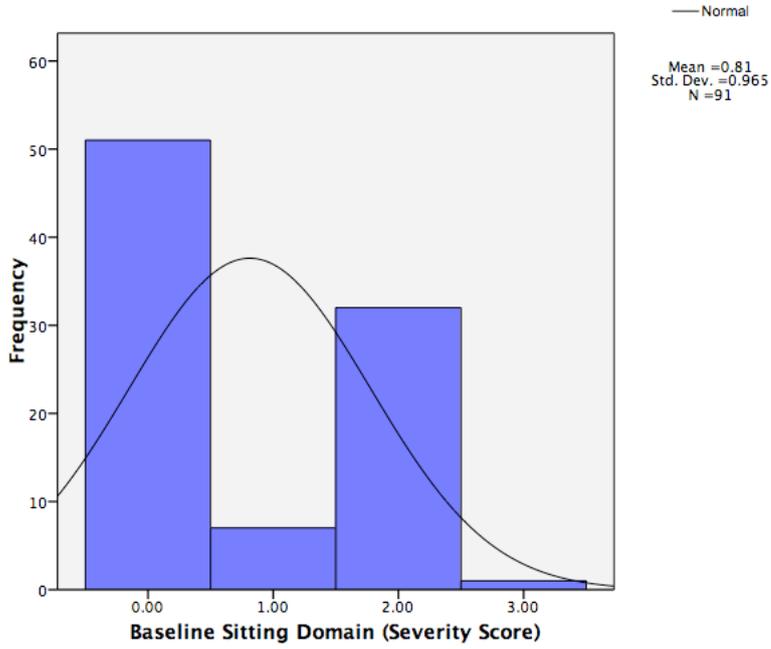
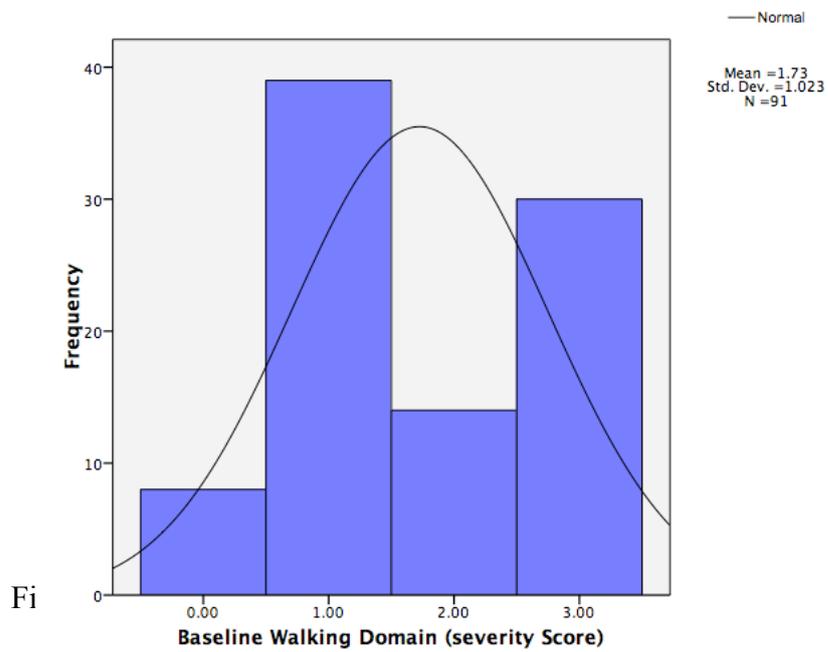


Figure D – 1.3: Baseline Walking domain histogram



Fi

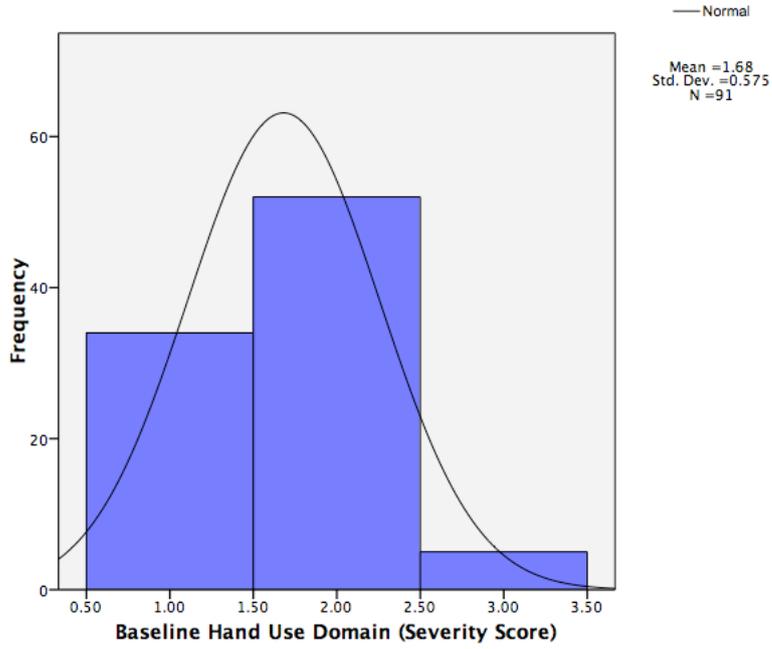


Figure D – 1.5: Baseline Speech domain histogram

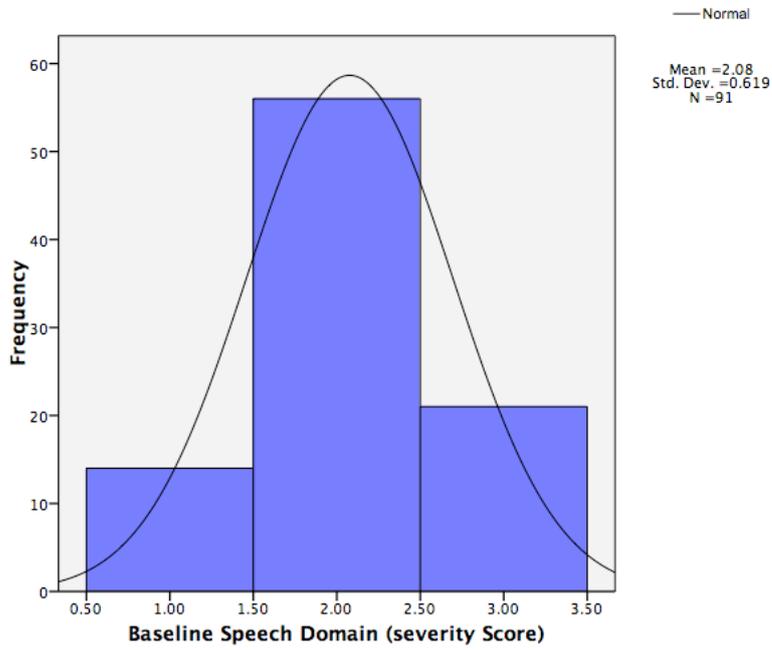


Figure D – 1.6: Baseline Epilepsy Domain histogram

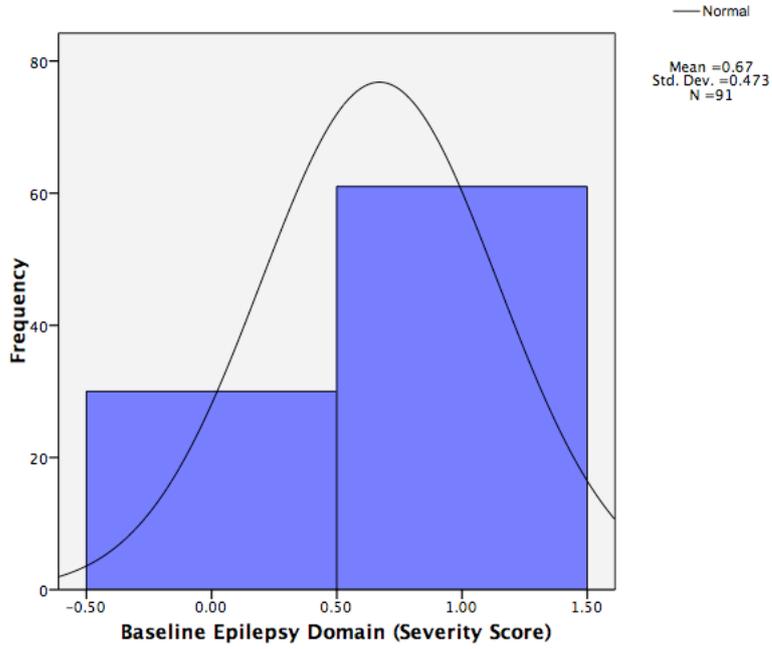
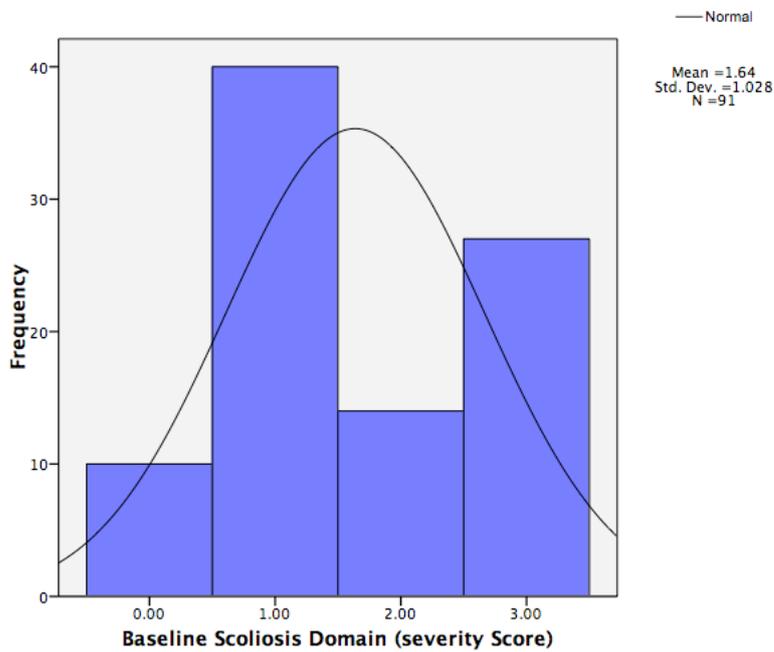


Figure D – 1.7: Baseline Scoliosis domain histogram



## Appendix D – 2: The Activity Questionnaire (AQ) normality tests

Table D – 2.1: AQ normality tests

	Kolmogorov-Smirnov (df)	Asymp sig. (2 tail)	Shapiro – wilk	Asymp. Sig. (2-Tailed)
AQ total	.115 (90)	.000	.898 (90)	.000
AQ Total Non verbal only	.149 (85)	.000	.906 (85)	.000
AQ: Overactivity sub-scale score for ALL participants	.117 (91)	.003	.932 (91)	.000
AQ Impulsivity sub-scale (Mobile)	.159 (48)	.004	.904 (48)	.001
AQ Impulsivity sub-scale (Immobile)	.419 (42)	.000	.547 (42)	.000
AQ Impulsivity sub-scale (All participants)	.198 (90)	.000	.812 (90)	.000

Figure D – 2.1: AQ Total (all participants verbal and Non verbal) Histogram

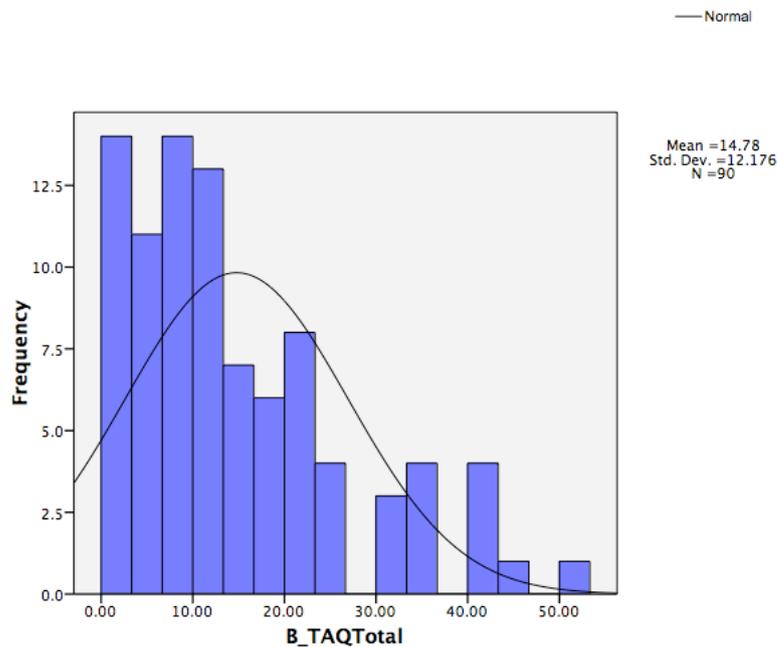


Figure D – 2.2: AQ Total for Non-Verbal participants histogram

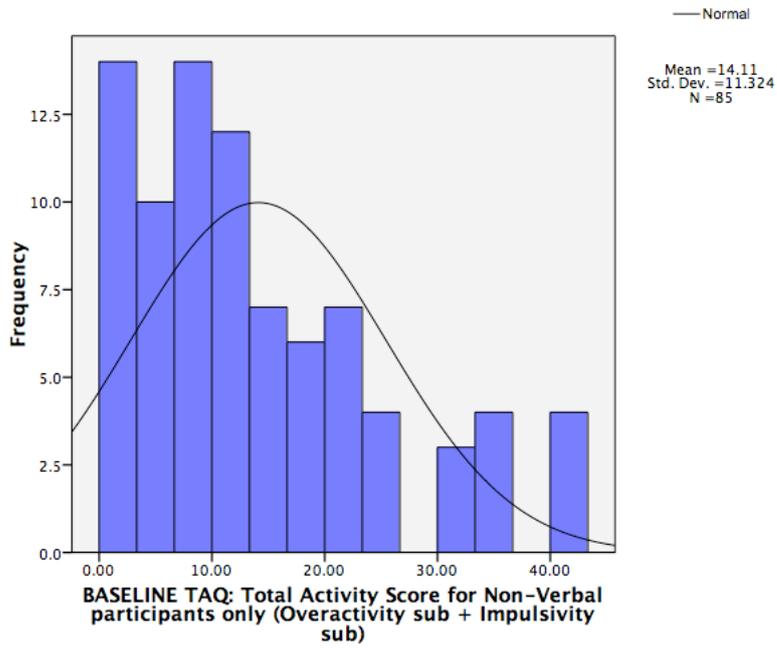


Figure D – 2.3: AQ Overactivity sub-scale histogram

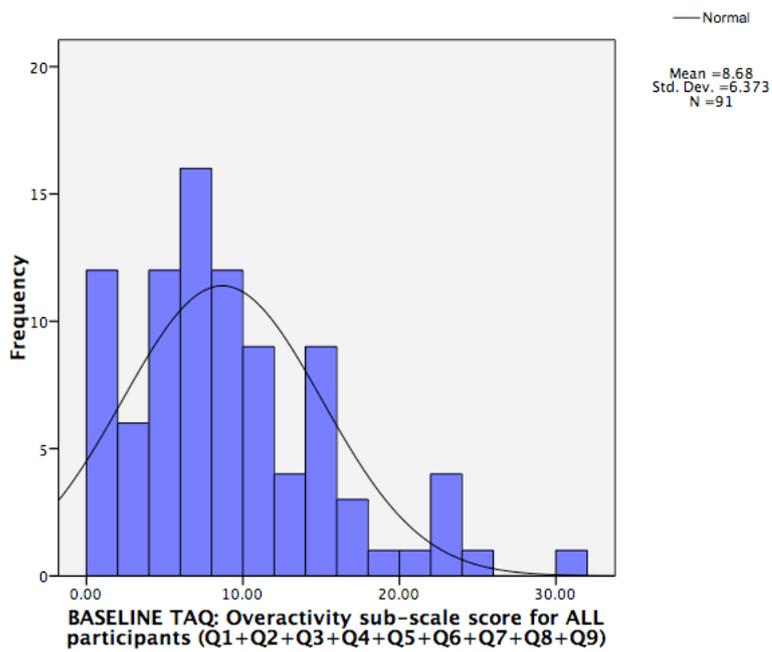


Figure D – 2.4: AQ impulsivity sub-scale for Mobile participants histogram

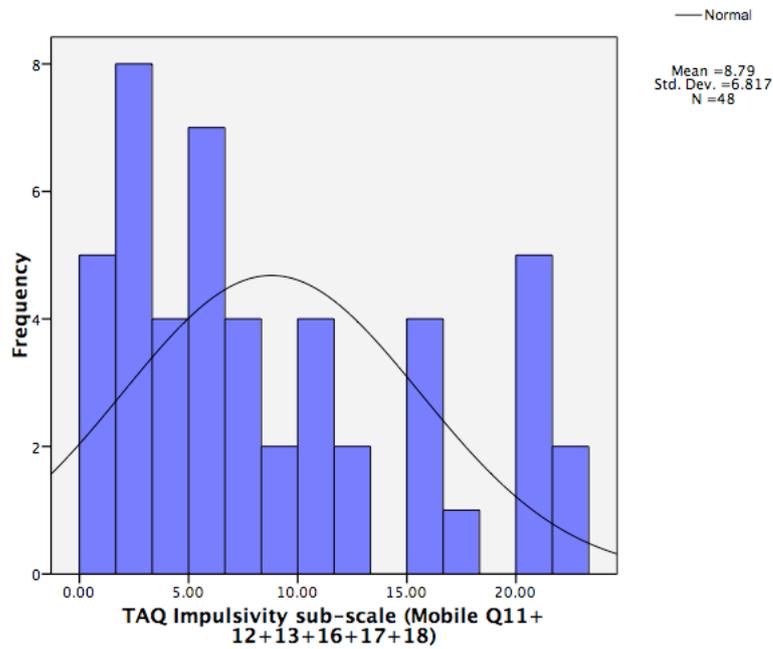


Figure D – 2.5: AQ Impulsivity sub-scale for Immobile participants histogram

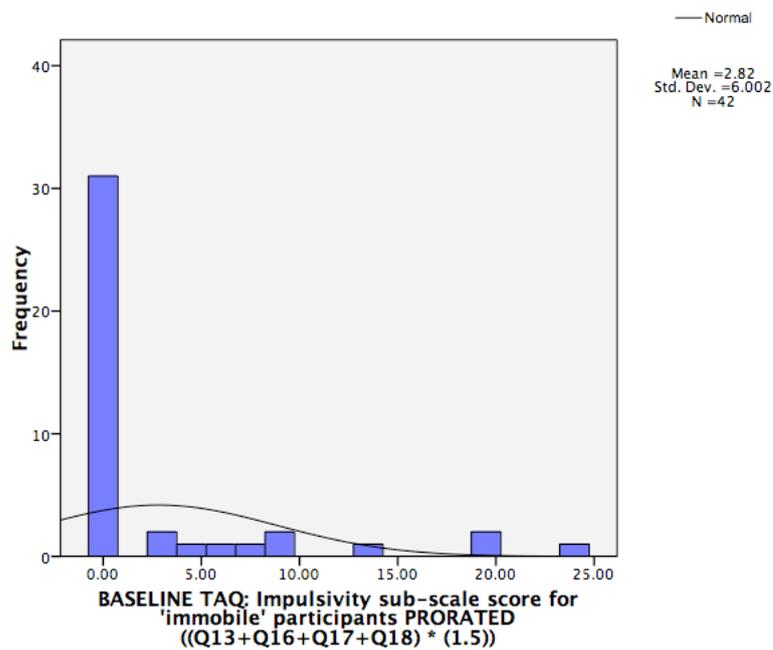
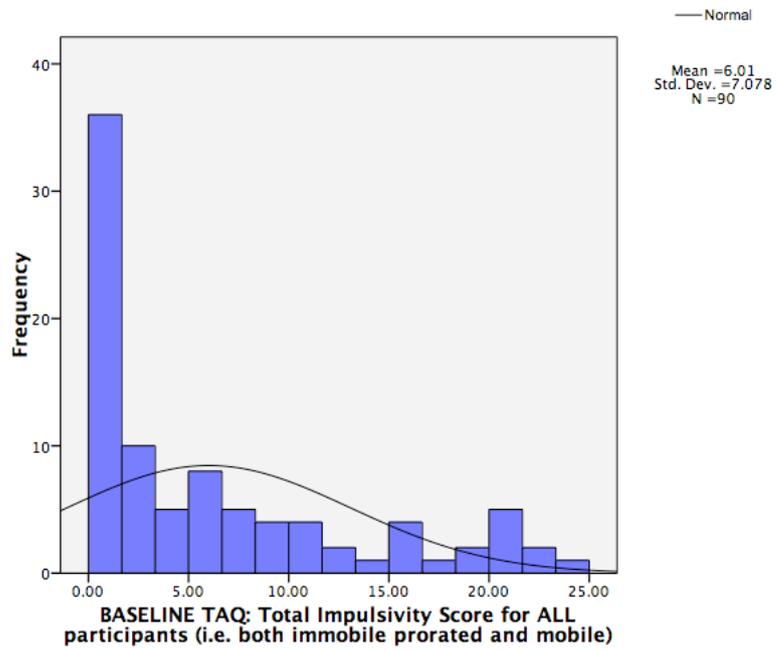


Figure D – 2.6: AQ Impulsivity sub-scale for All participants histogram



**Appendix D – 3: Mood, Interest & Pleasure Questionnaire (MIPQ – S) normality tests**

Table D – 3.1: MIPQ – S Normality tests

	Kolmogorov-Smirnov (df)	Asymp sig. (2 tail)	Shapiro-Wilk (df)	Asymp sig. (2 tail)
Mood, Interest and Pleasure Questionnaire Total score	.114 (90)	.006	.983(90)	.299
Baseline MIPQ-S: Mood subscale	.127 (90)	.001	.955(90)	.003
Baseline MIPQ-S: Interest and Pleasure subscale total score	.076 (90)	.200*	.977(90)	.111

Figure D – 3.1: MIPQ – S total score histogram with normality curve

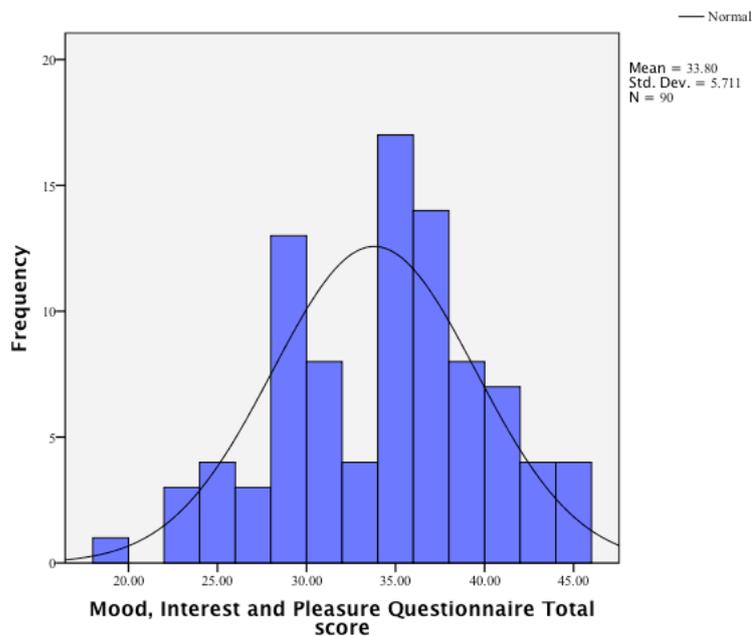


Figure D – 3.2: MIPQ – S Mood subscale histogram with normality curve

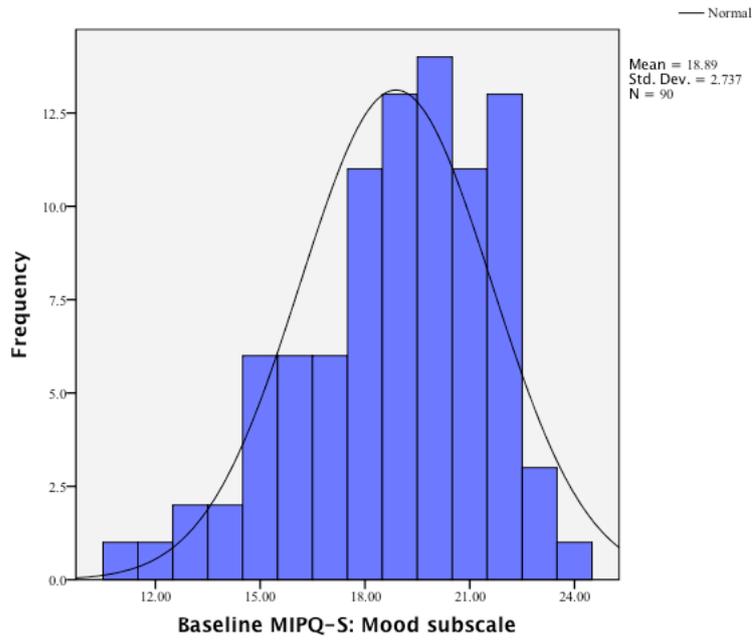
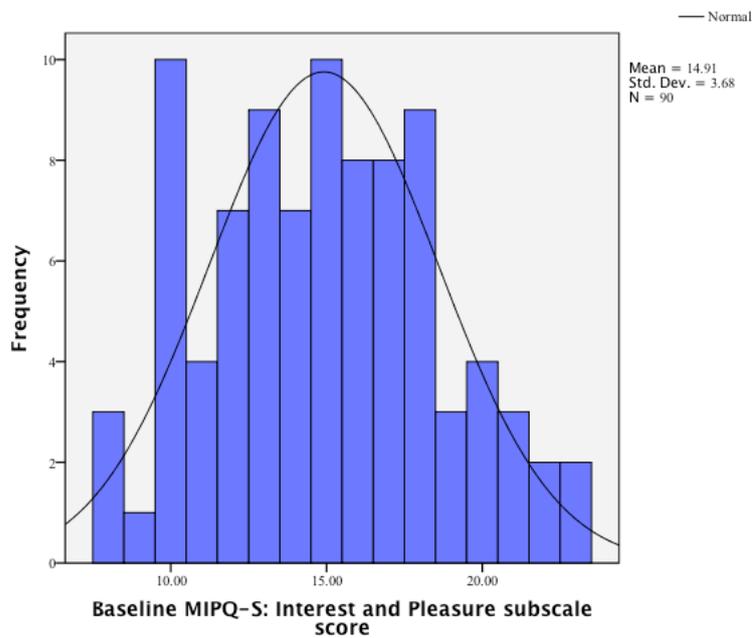


Figure D – 3.3: MIPQ – S Interest & Pleasure subscale histogram with normality curve



## Appendix D – 4: Rett Syndrome Behavioural Questionnaire (RSBQ) Normality tests

Table D – 4.1: RSBQ Normality tests

	Kolmogorov-Smirnov (df)	Asymp sig. (2 tail)	Shapiro-Wilk (df)	Asymp sig. (2 tail)
RSBQ Total Score	.079 (90)	.200	.986 (90)	.446
RSBQ General Mood	.112 (90)	.007	.952 (90)	.002
RSBQ Breathing Problem	.107 (90)	.013	.943 (90)	.001
RSBQ Hands behaviour	.171 (90)	.000	.909 (90)	.000
RSBQ Repetitive face movements	.147 (90)	.000	.950 (90)	.002
RSBQ Body rocking and expressionless face	.130 (90)	.001	.961 (90)	.008
RSBQ Night-Time behaviour	.224 (90)	.000	.877 (90)	.000
RSBQ Fear/Anxiety	.118 (90)	.003	.951 (90)	.002
RSBQ Walking/Standing	.292 (90)	.000	.795 (90)	.000

Figure D – 4.1: RSBQ Total score histogram with normality curve

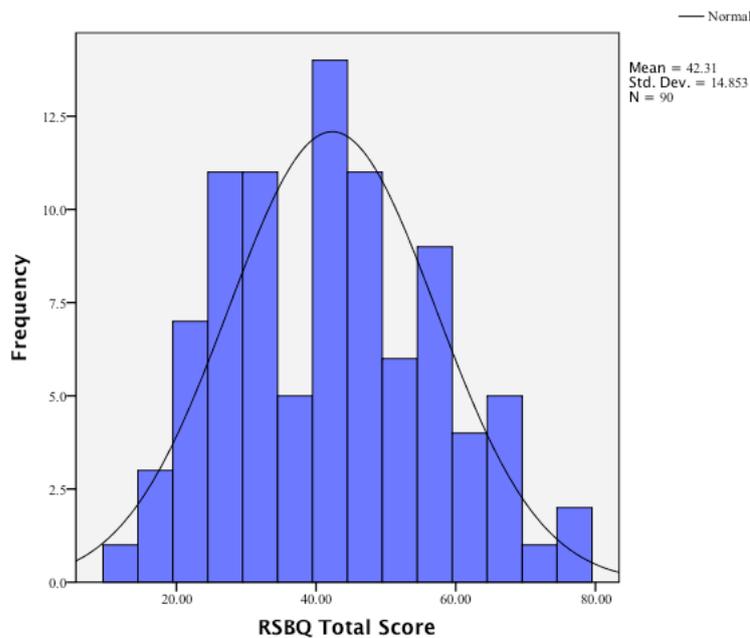


Figure D – 4.2: RSBQ General mood histogram with normality curve

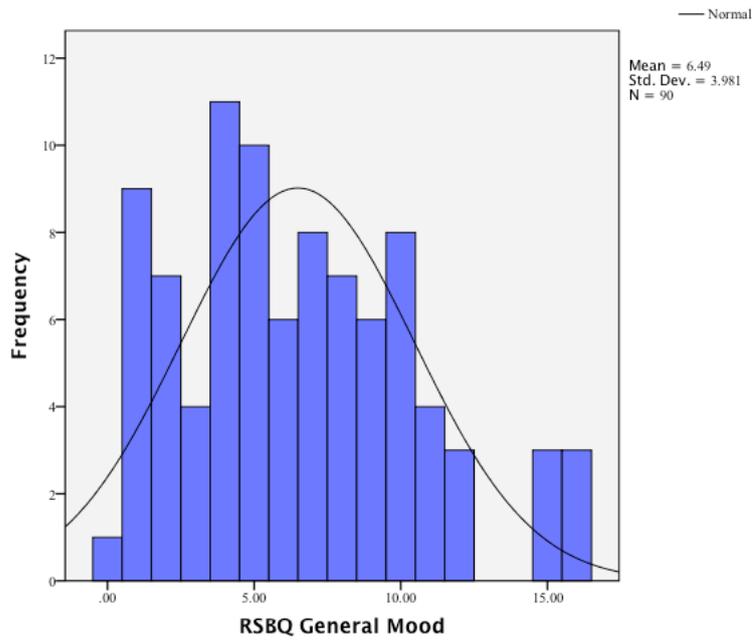


Figure D – 4.3: RSBQ Breathing abnormalities histogram with normality curve

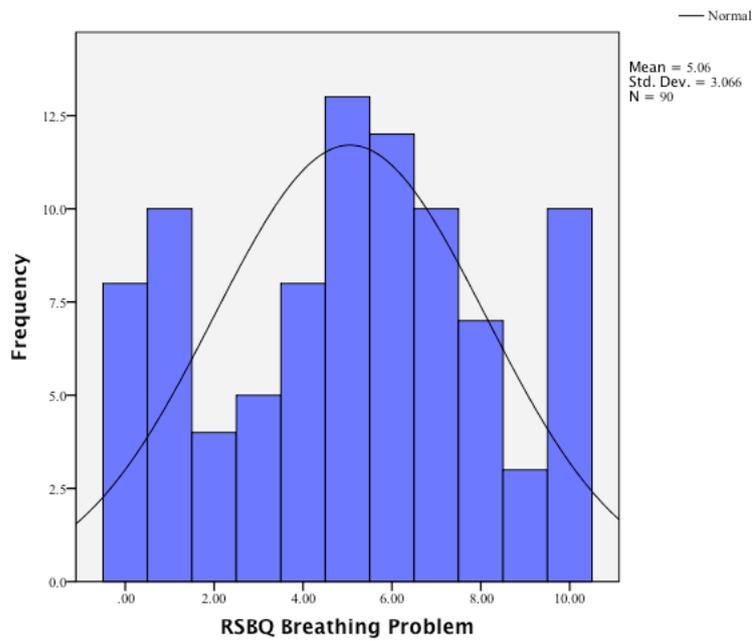


Figure D – 4.4: RSBQ Hand behaviour histogram with normality curve

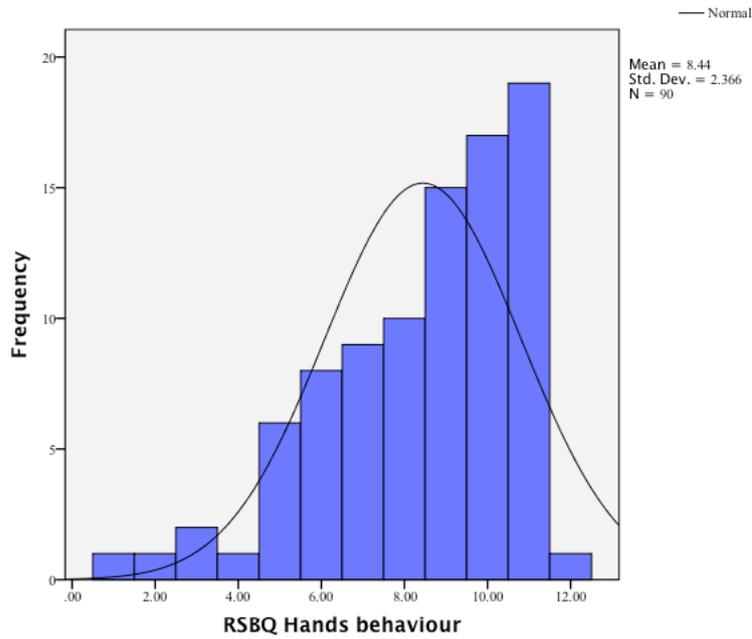


Figure D – 4.5: RSBQ Repetitive face movements histogram with normality curve

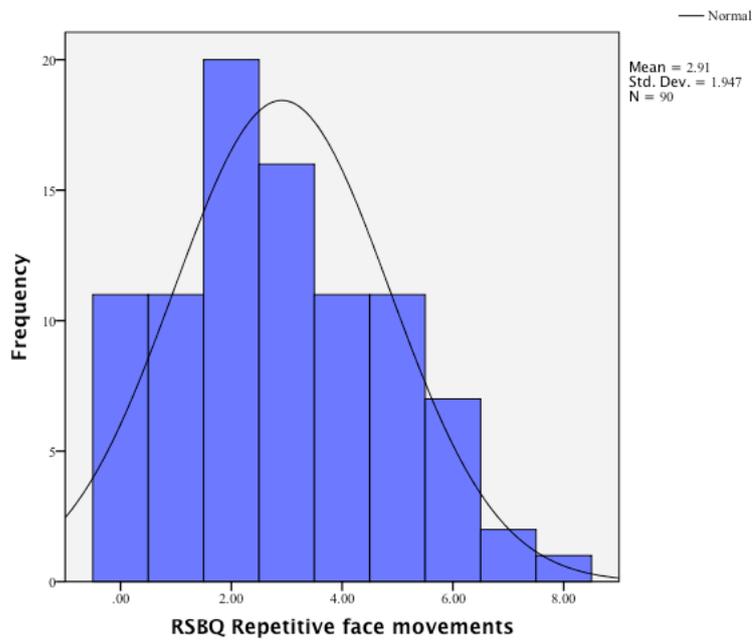


Figure D – 4.6: RSBQ Body rocking and Expressionless face histogram with normality curve

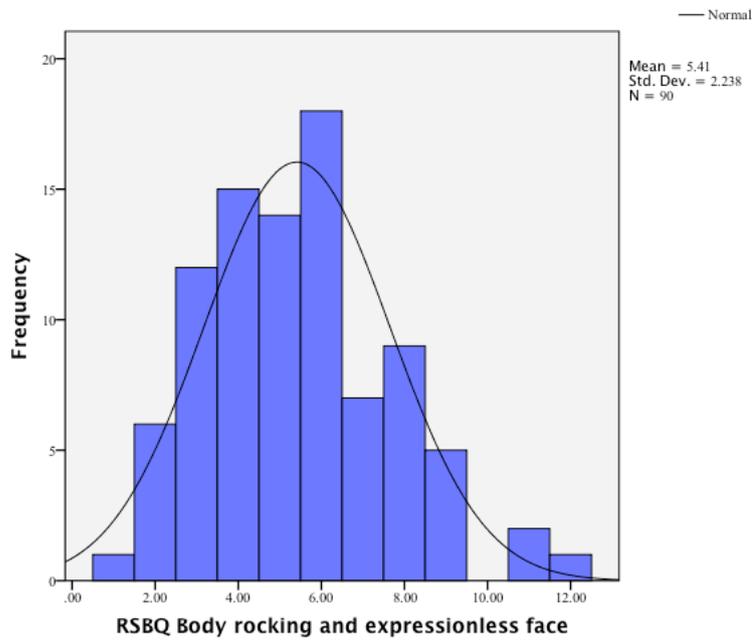


Figure D – 4.7: RSBQ Night-Time behaviour histogram with normality curve

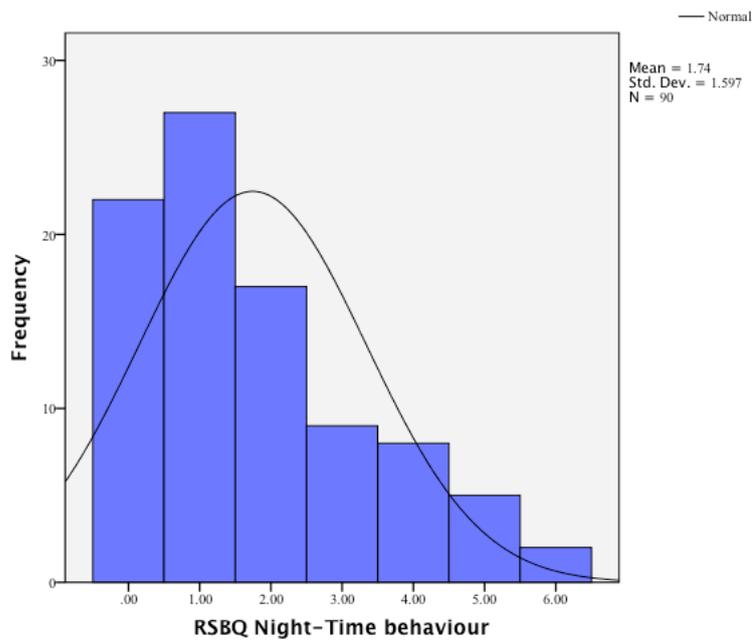


Figure D – 4.8: RSBQ Fear & Anxiety histogram with normality curve

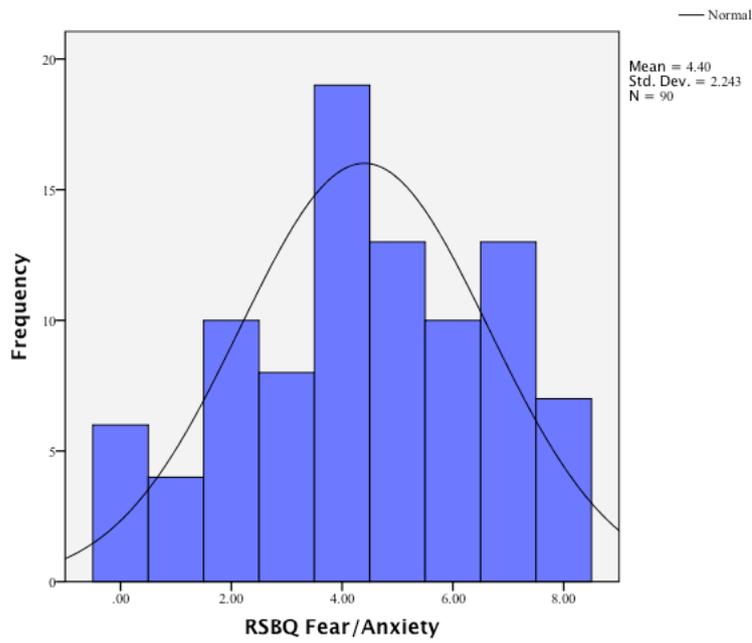
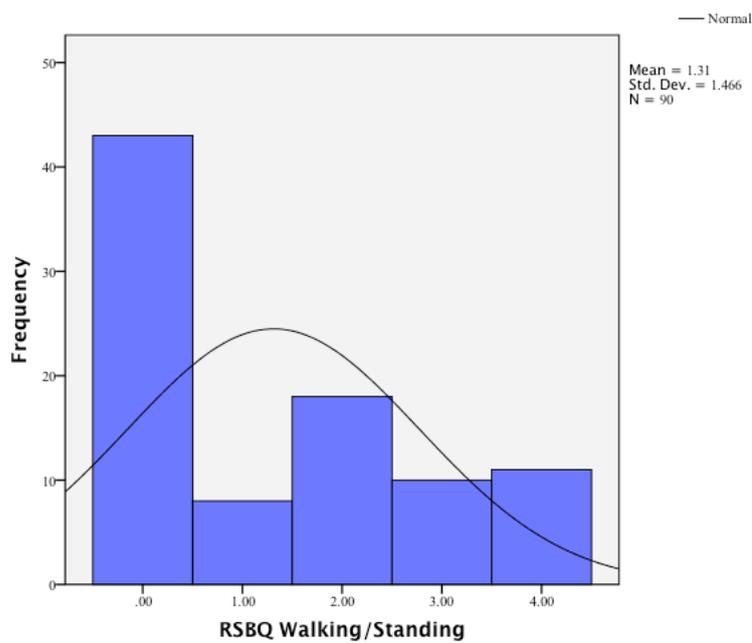


Figure D – 4.9: RSBQ Walking & Standing histogram with normality curve



## Appendix D – 5: Repetitive Behaviour Questionnaire (RBQ) Normality tests

Table D – 5.1: RBQ Normality tests

	Kolmogorov-Smirnov (df)	Asymp sig. (2 tail)	Shapiro – Wilk	Asymp sig. (2 tail)
RBQ Total (All participants)	.206 (91)	.000	.783 (91)	.000
RBQ stereotyped Behaviour	.167 (91)	.000	.939 (91)	.000
RBQ Compulsive Behaviour	.526 (91)	.000	.102 (91)	.000
RBQ Insistence on Sameness	.481 (91)	.000	.492 (91)	.000

Figure D – 5.1: RBQ Total (All Participants) histogram with normality curve

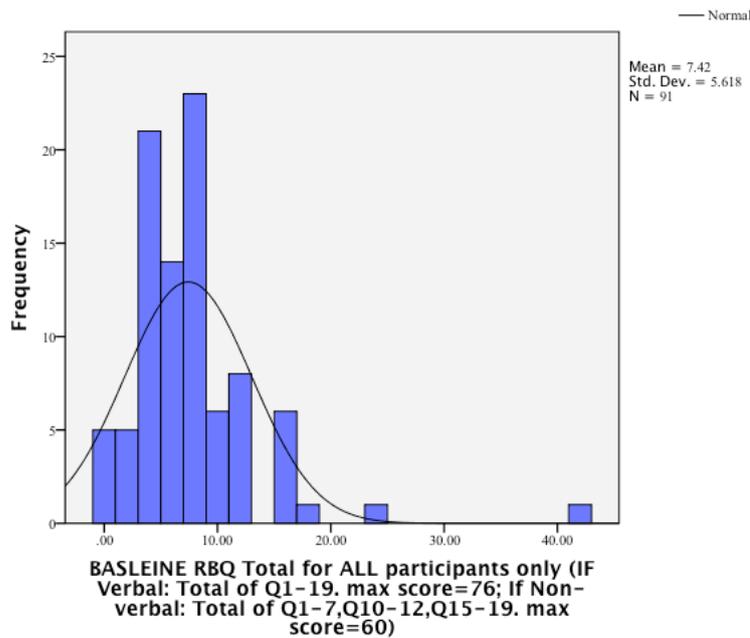


Figure D – 5.2: RBQ Stereotyped Behaviour histogram with normality curve

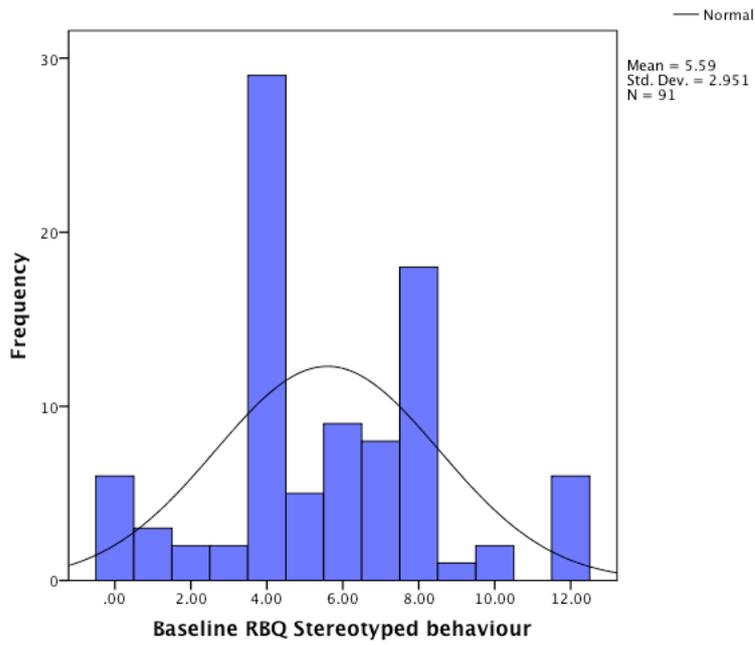


Figure D – 5.3: RBQ Compulsive Behaviour histogram with normality curve

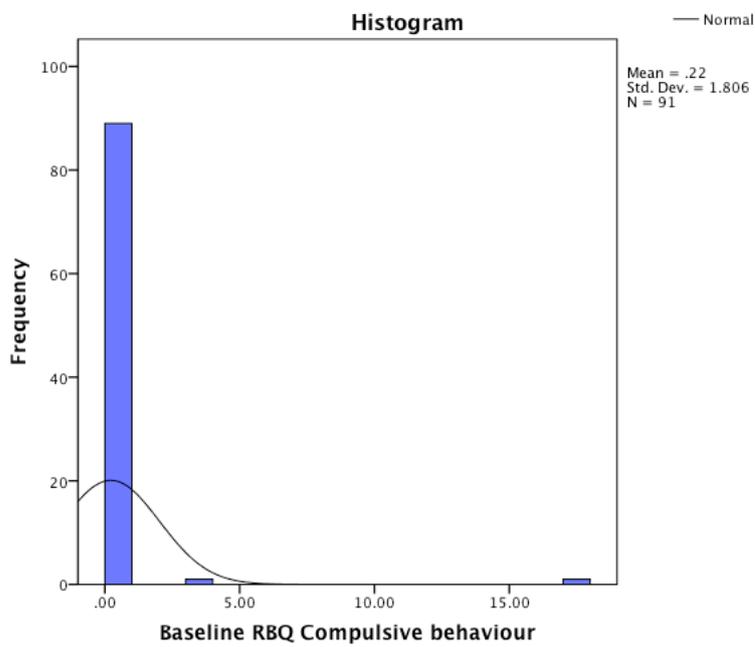
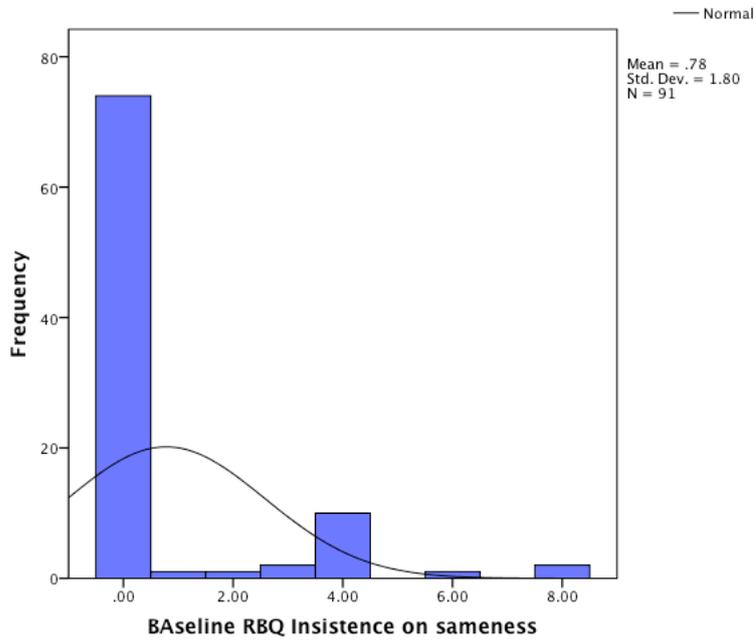


Figure D – 5.4: RBQ insistence on Sameness histogram with normality curve



## Appendix D – 6: Developmental Behavior Checklist (DBC) Normality tests

	Kolmogorov-Smirnov (df)	Asymp sig. (2 tail)	Shapiro – Wilk	Asymp sig. (2 tail)
DBC Total	.128 (87)	.001	.931 (87)	.000
DBC Disruptive subscale	.222 (87)	.000	.846 (87)	.000
DBC self-Absorbed subscale	.129 (87)	.001	.900 (87)	.000
DBC Communication subscale	.260 (87)	.000	.694 (87)	.000
DBC Anxiety subscale	.253 (87)	.000	.708 (87)	.000
DBC Social subscale	.169 (87)	.000	.897 (87)	.000
DBC Depressive subscale (Adult)	.217 (46)	.000	.901 (46)	.001

Figure D – 6.1: DBC Total histogram with normality curve

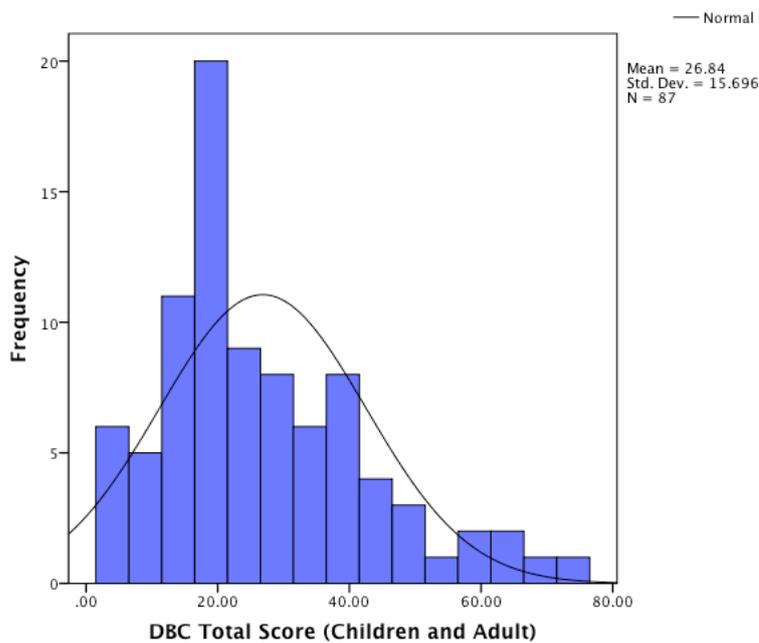


Figure D – 6.2: DBC Disruptive subscale histogram with normality curve

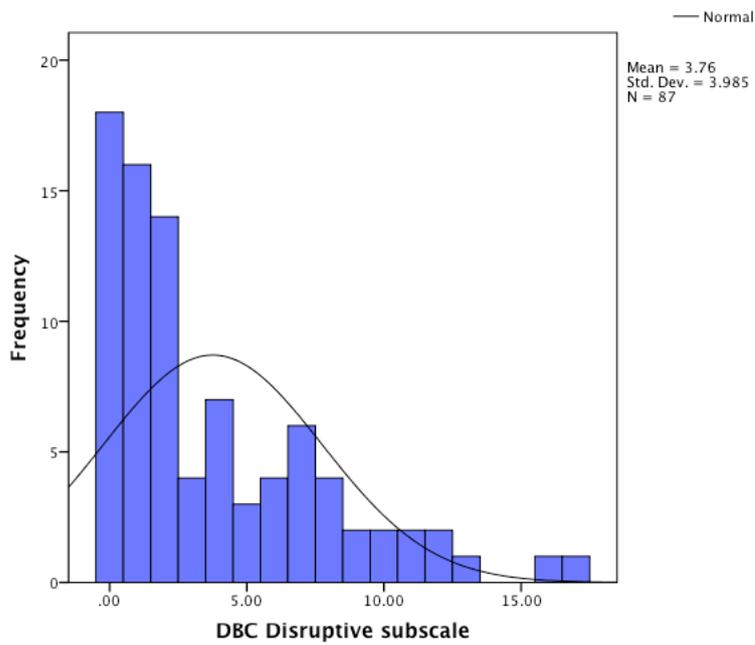


Figure D – 6.3: DBC Self-Absorbed subscale histogram with normality curve

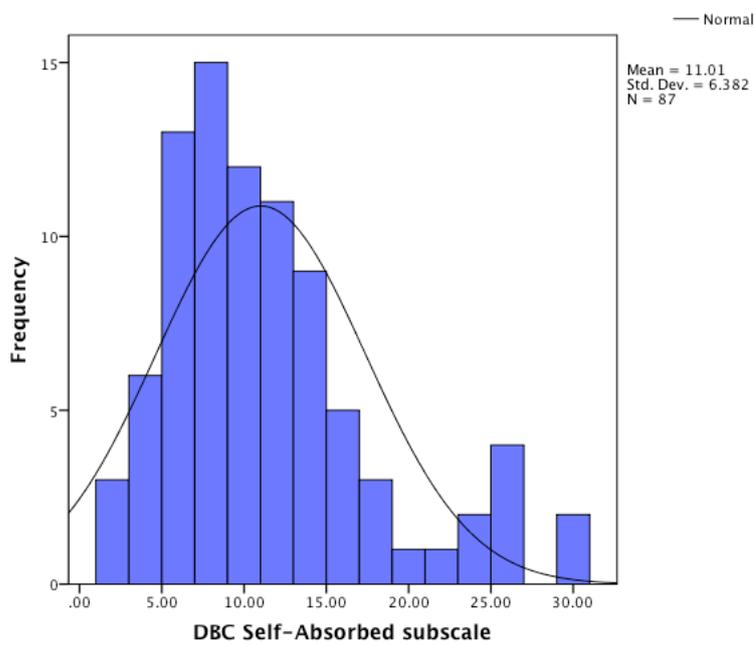


Figure D – 6.4: DBC Communication subscale histogram with normality curve

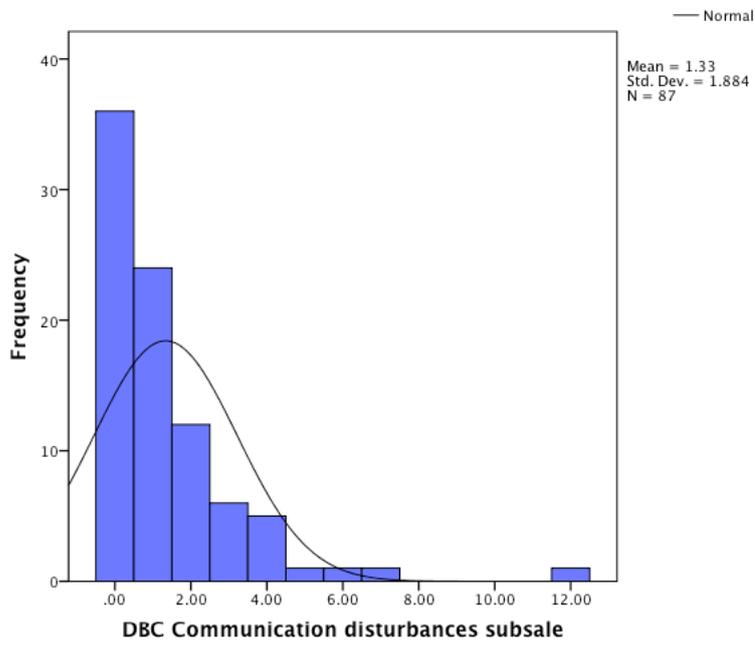


Figure D – 6.5: DBC Anxiety subscale histogram with normality curve

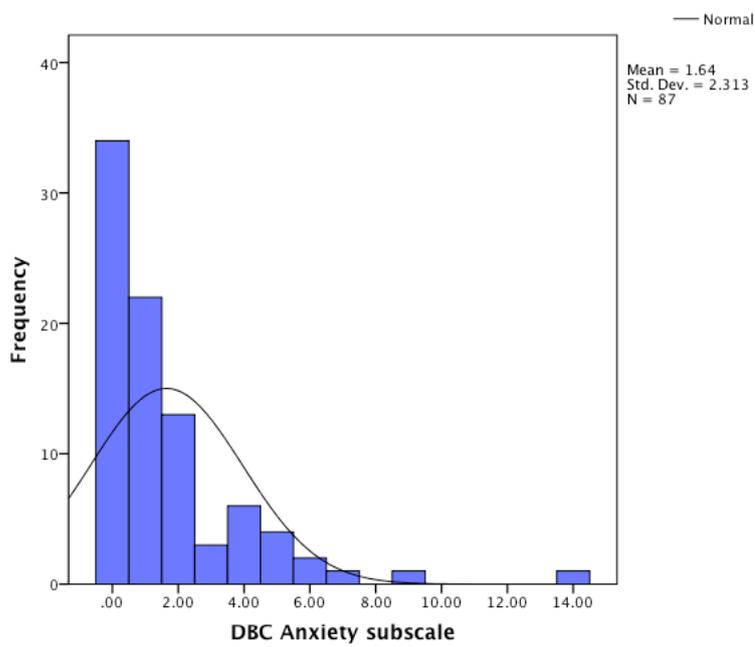


Figure D – 6.6: DBC Social subscale histogram with normality curve

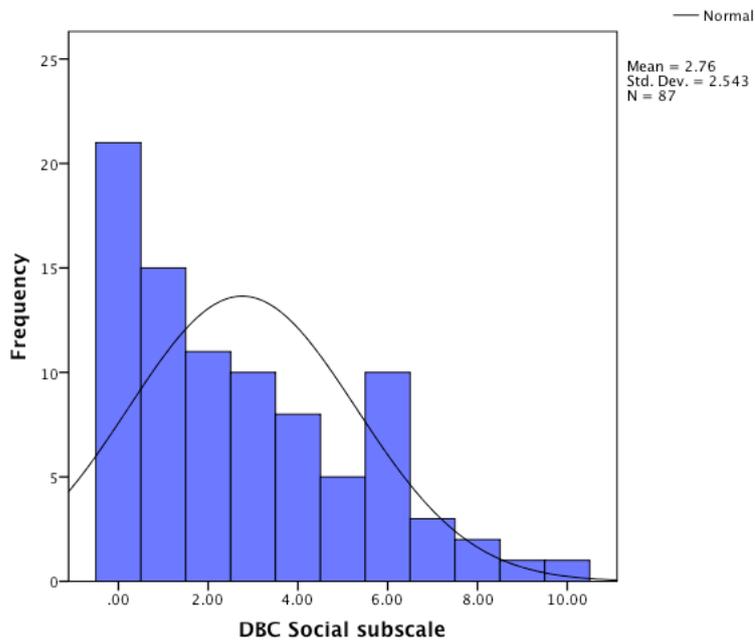
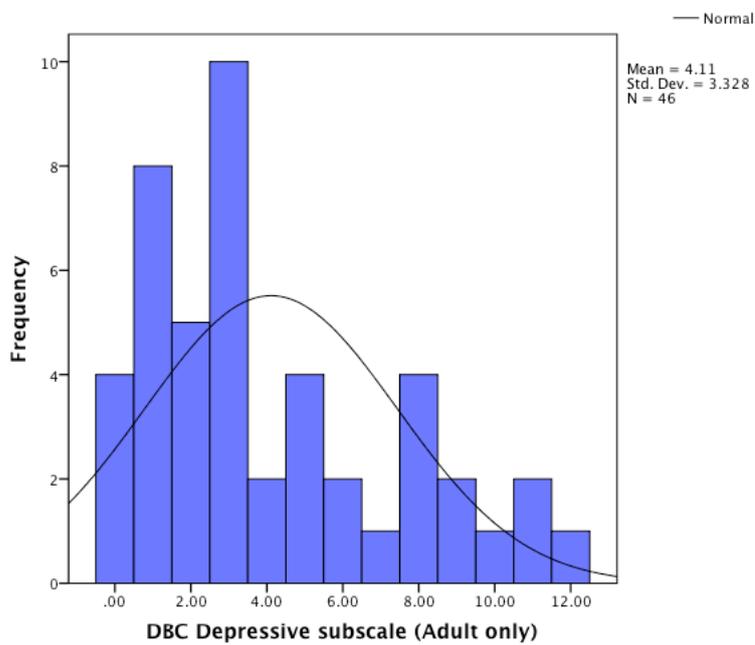


Figure D – 6.7: DBC Depressive subscale (Adult) histogram with normality curve



## Appendix D – 7: Family measure (QRS, PGS and HADS) Normality Tests

	Kolmogorov-Smirnov (df)	Asymp sig. (2 tail)	Shapiro – Wilk	Asymp sig. (2 tail)
(QRS) Family stress Total score	.094 (87)	.057	.972 (87)	.059
(Baseline) Positive Gain Scale Total score	.143 (87)	.000	.913(87)	.000
(HADS) Anxiety	.107 (87)	.015	.975 (87)	.084
HADS) Depression	.134 (87)	.001	.932 (87)	.000
(Baseline)Positive Affect Scale Total Score	.098 (87)	.038	.973 (87)	.069

Figure D – 6.1: Questionnaire on Resources and stress (QRS) histogram with normality curve

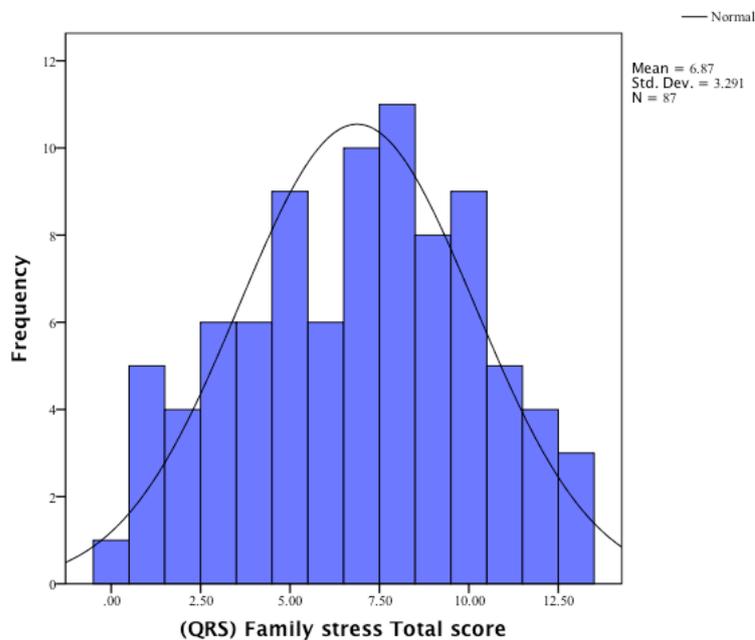


Figure D – 6.2: Positive Gain Scale (PGS) histogram with normality curve

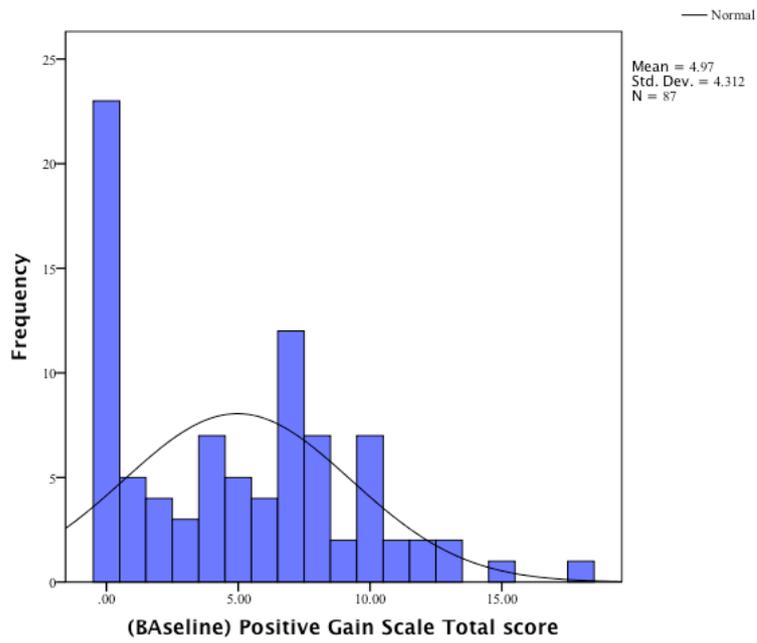


Figure D – 6.3: Anxiety subscale of the Hospital Anxiety and Depression scale (HADS) histogram with normality curve

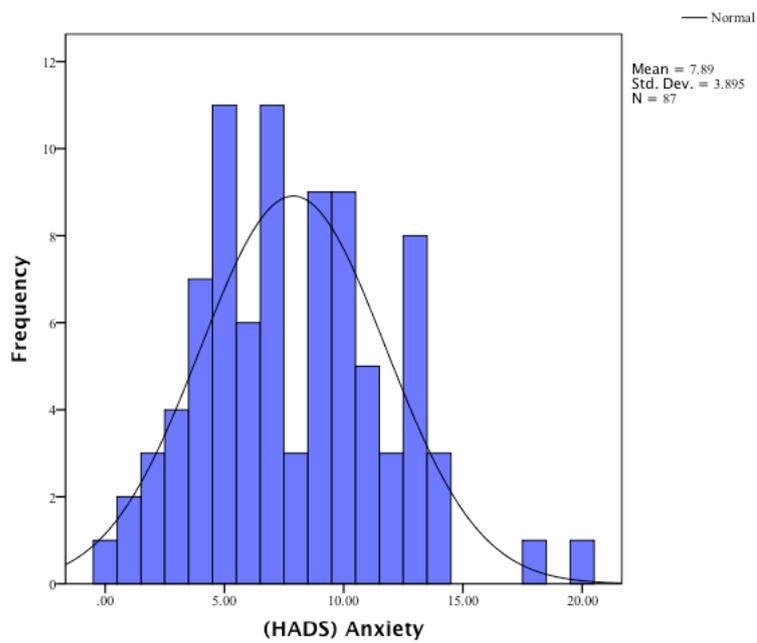


Figure D – 6.4: Depression subscale of the Hospital Anxiety and Depression scale (HADS) histogram with normality curve

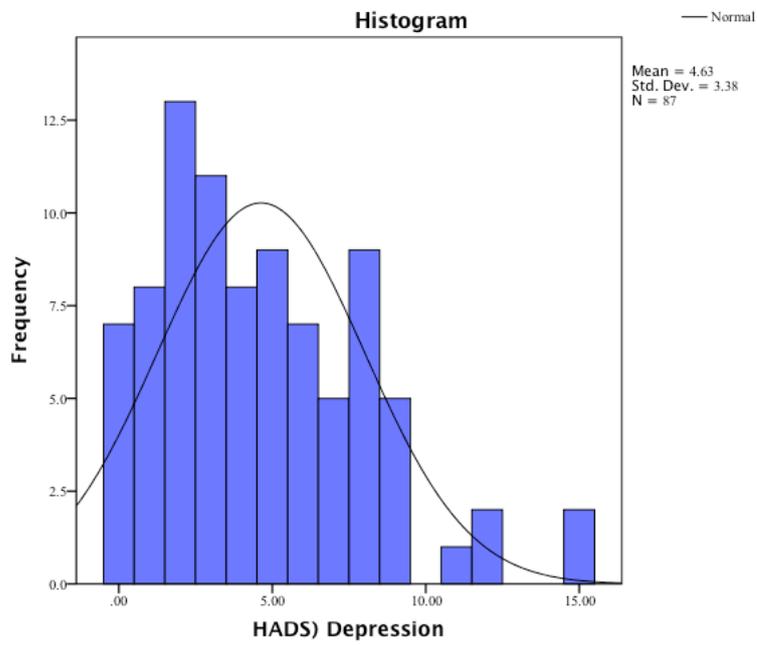
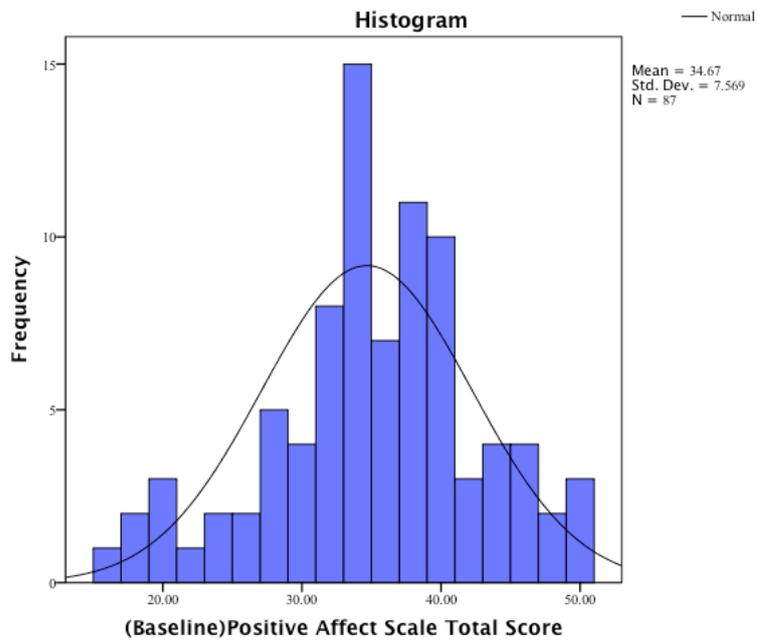


Figure D – 6.5 Positive affect scale (PANAS) histogram with normality curve

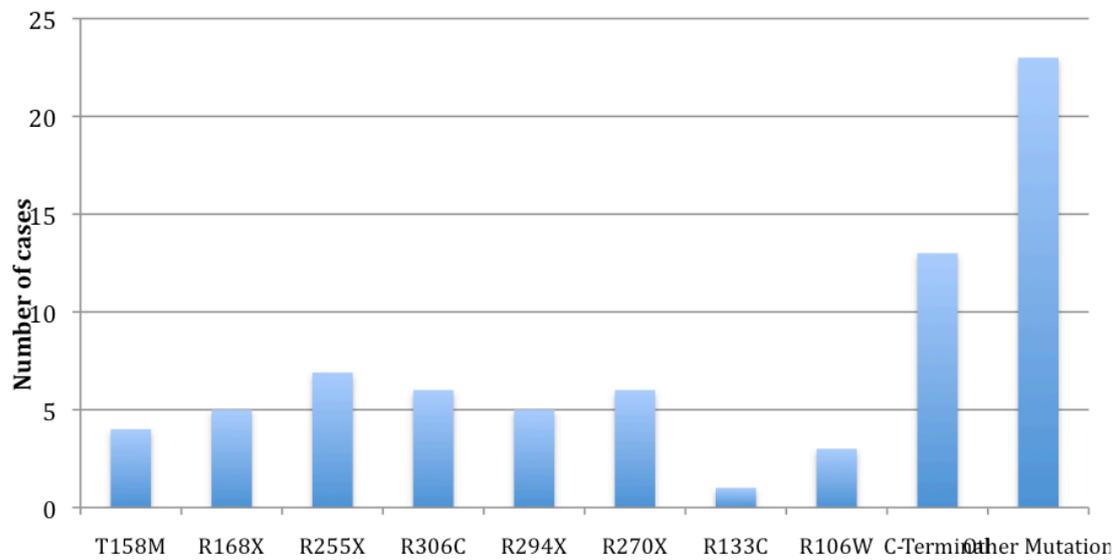


## **APPENDIX – E: GENETIC MUTATIONS AND SEVERITY SCORE**

### Appendix E – 1: Most common single mutations

Type of mutations included in the ‘other Mutations category’ included: R306C (3), P302R, P101L, Q244X, F155C, Y141X, Q128X, K289X (1), P152R (4), c.710delGG237fsX10 (1), c.116delGA (1), c.695delGG232fsx15 (1), c.617delGG206fsx3 (1), c.467insCF157fsX174 (1), c.1133d'E (1), c.241\_242del2bp (Mosaic) G81fsX7 (Mosaic) (1), c.856\_859delAAAG K285fsX286 (1).

Figure E – 1: Most common single mutations



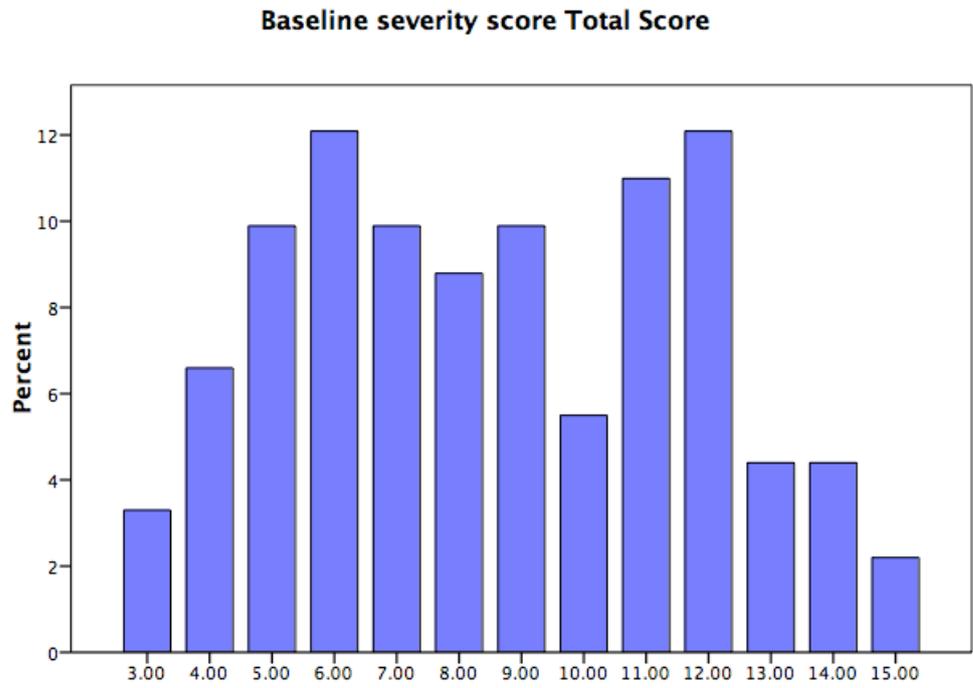
## Appendix E – 2: TYPE AND LOCATION OF MUTATIONS IN THE SAMPLE

**Table E – 1: Type and Location of mutations**

Large Deletion	C-Terminal	Early Truncating	Missense	Late Truncating
Deletion, Exon3 and 4 (2)	c.1097_1284del188 (1)	R168X (6)	T158M (4)	R294X (5)
	c.1157_1200del144 bp (1)	R270X (6)	R306H (3)	K289X (1)
	c.1324_1367del44bp (1)	Q244X (1)	P302R (1)	c.856_859delAAAG K285fsX286 (1)
	c.1152_1192del41bpP385fsX390 (1)	c.710delGG237fsX10 (1)	P152R (4)	
	c.1164_1207del44bpP389X (3)	R255X (5)	P101L (1)	
	c.1116_1201del86bpH372fsX373 (1)	Y141X (1)	F155C (1)	
	c.1126_1159del34bpins28P376fsX400 (1)	Q128X (1)	R133C (1)	
	c.1157_1188del32bpL386fsX394 (1)	c.116delGA (1)	R306C (6)	
	44 base pair deletion, exon 4 (1)	c.695delGG232fsx15 (1)	R106W (1)	
	c.1150_1153del4bpP385fsX407 (1)	c.617delGG206fsx3 (1)	c.1133d'E (1)	
	1169-1172del11bp (1)	c.467insCF157fsX174 (1)		
		Q47X (1)		
		c.241_242del2bp (Mosaic) G81fsX7 (Mosaic) (1)		

### Appendix E – 3: Total and domains severity score

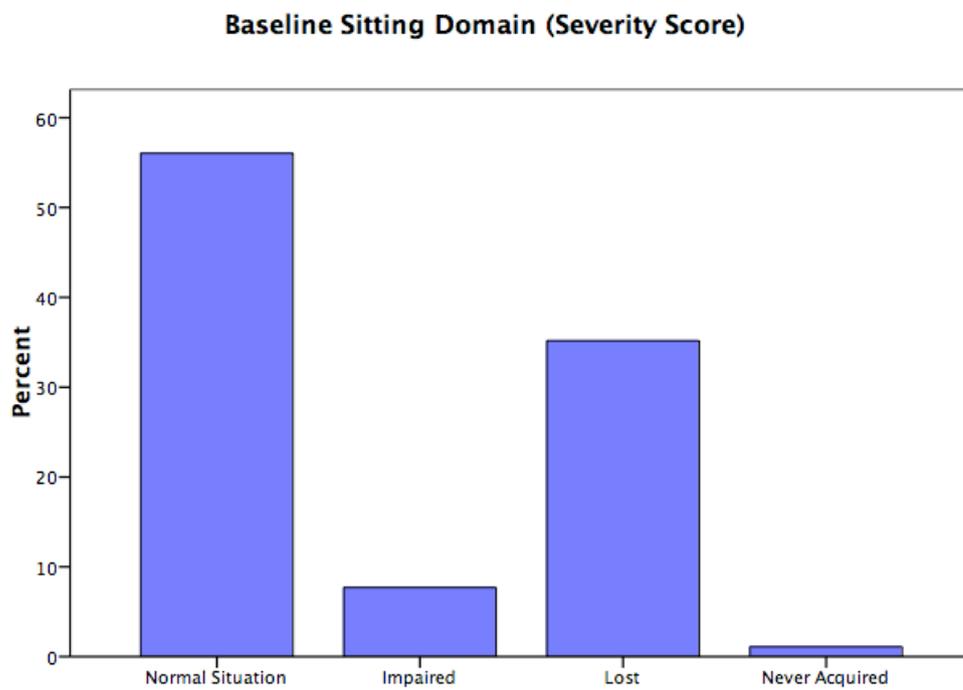
Figure E – 2: Total and domains severity score



**Table E – 2: Baseline Sitting domain (severity score)**

	<b>Normal Situation</b>	<b>Never Acquired</b>	<b>Impaired</b>	<b>Lost</b>	<b>Total</b>
N (%)	51 (56.0)	1 (1.1)	7 (7.7)	32 (35.2)	91 (100)

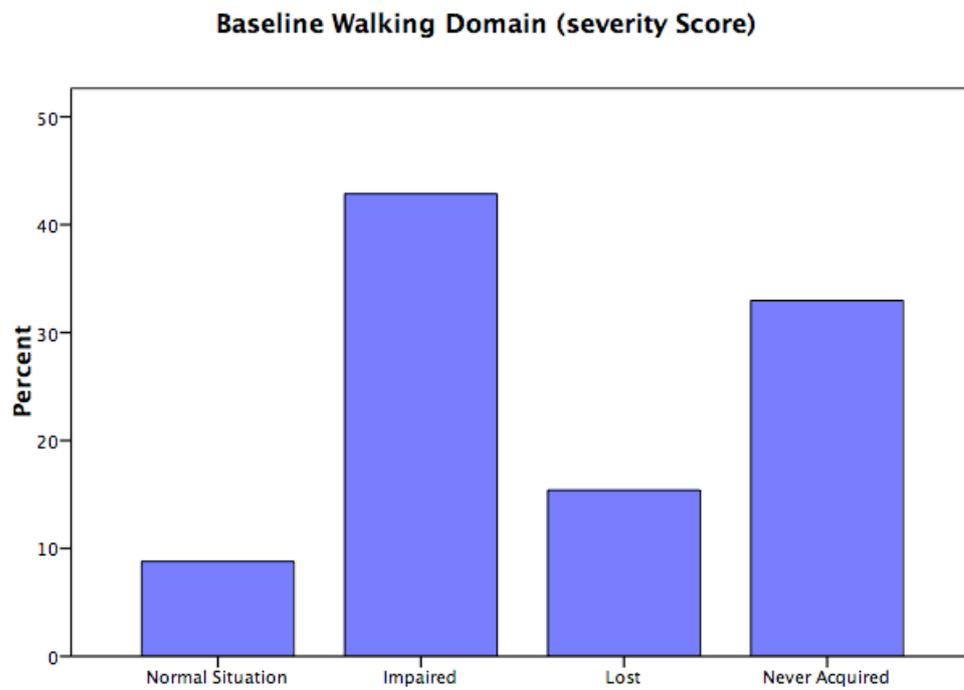
**Figure E – 3: Sitting Domain**



**Table E – 3: Baseline Walking domain (Severity score)**

	<b>Impaired</b>	<b>Lost</b>	<b>Never Acquired</b>	<b>Normal Situation</b>	<b>Total</b>
<b>N (%)</b>	39 (42.9)	14 (15.4)	30 (33.0)	8 (8.8)	91 (100)

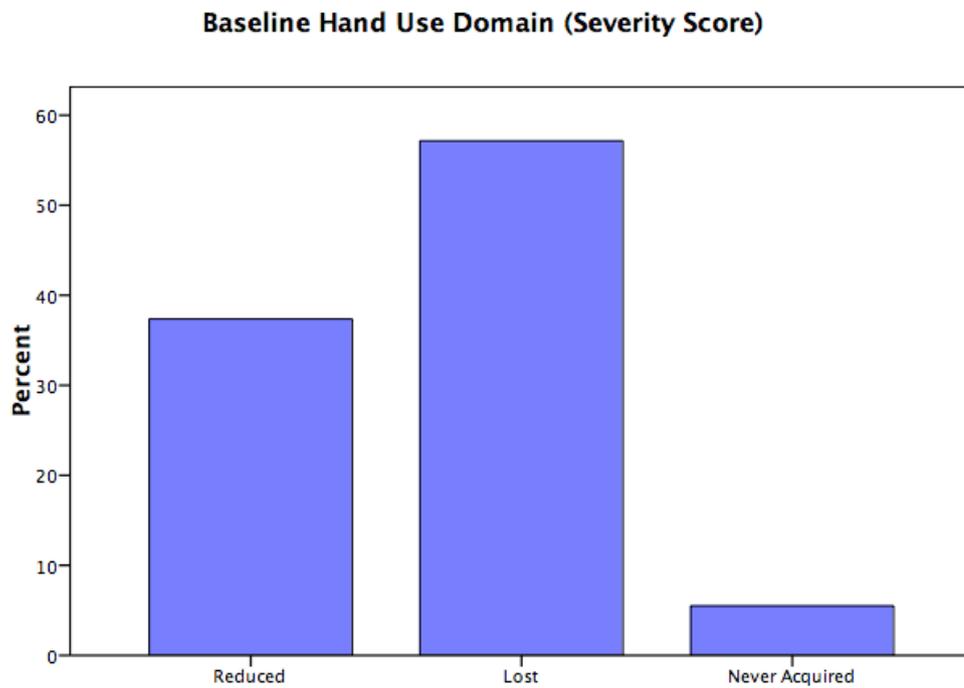
**Figure E – 4: Walking Domain**



**Table E – 4: Baseline Hand use domain (severity score)**

	<b>Reduced</b>	<b>Lost</b>	<b>Never Acquired</b>	<b>Total</b>
N (%)	34 (37.4)	52 (57.1)	5 (5.5)	91 (100)

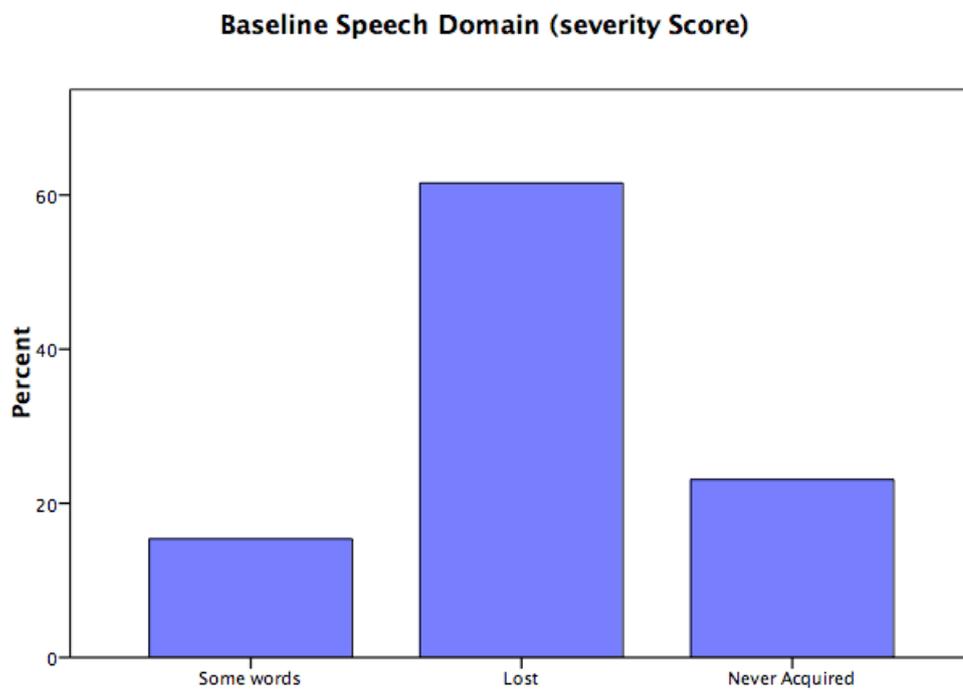
**Figure E – 5: Hand use domain**



**Table E – 5: Baseline Speech domain (severity score)**

	<b>Some words</b>	<b>Lost</b>	<b>Never Acquired</b>	<b>Total</b>
<b>N (%)</b>	14 (15.4)	56 (61.5)	21 (23.1)	91 (100)

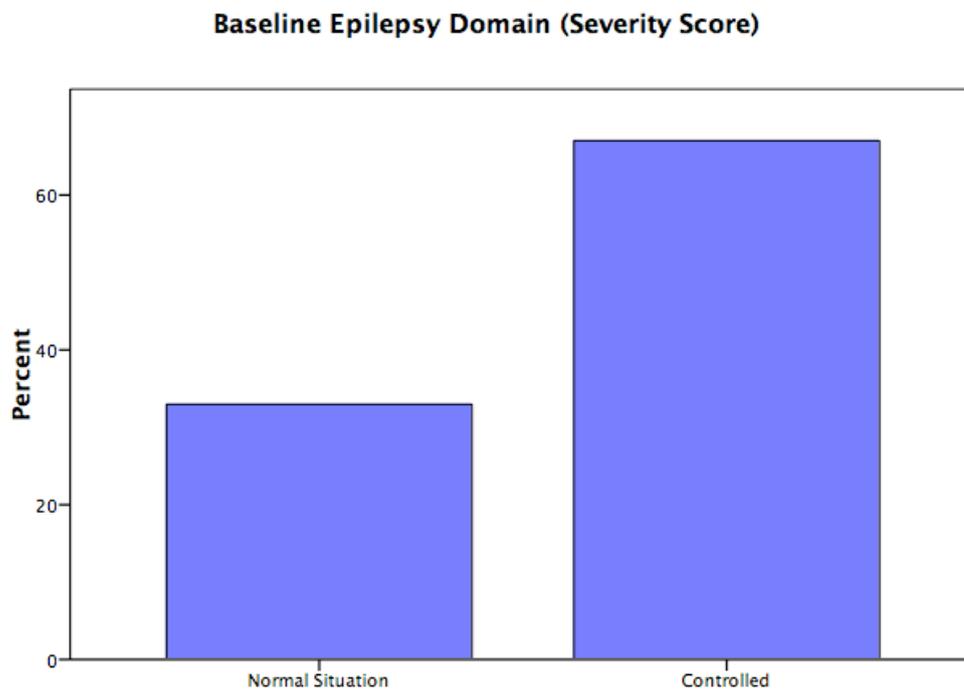
**Figure E – 6: Speech domain**



**Figure E – 6: Baseline Epilepsy domain (severity score)**

	<b>Normal Situation</b>	<b>Controlled</b>	<b>Total</b>
<b>N (%)</b>	30 (33)	61(67)	91 (100)

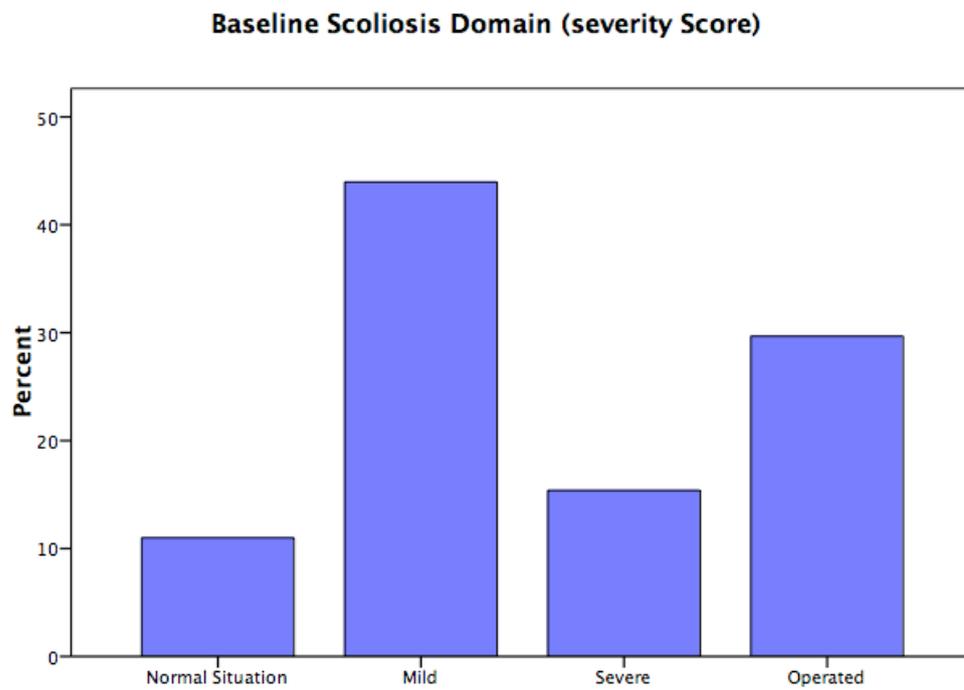
**Figure E – 6: Epilepsy domain**



**Table E – 7: Baseline Scoliosis domain (severity score)**

	<b>Normal Situation</b>	<b>Mild</b>	<b>Severe</b>	<b>Operated</b>	<b>Total</b>
Frequency	10 (11.0)	40 (44.0)	14 (15.4)	27 (29.7)	91 (100)

**Figure E – 8: Scoliosis domain**



**APPENDIX F**  
**CORRELATION ANALYSIS FOR FAMILY MEASURES**

**0 for RSBQ and family scales (QRS, HADS anxiety, HADS Depression)**

	<b>QRS</b>	<b>Anxiety</b>	<b>Depression</b>
<b>RSBQ Total Score</b>	.266**	.302*	.258**
<b>General Mood</b>	.354*	.236**	.340*
<b>Breathing problem</b>	.069	.206	-.054
<b>Hands behaviour</b>	.029	.085	.082
<b>Face movements</b>	.073	.229**	.123
<b>Body rocking and Expressionless face</b>	.126	.175	.231**
<b>Night time behaviour</b>	.059	.185	.047
<b>Fear/anxiety</b>	.246**	.366*	.198
<b>Walking/standing</b>	.246	.366	.198

\*p < .005, \*\*p < .05

#### Appendix F – 2: Correlation coefficients for RSBQ and PGS and PAS

	<b>PGS</b>	<b>PAS</b>
<b>RSBQ Total Score</b>	.022	-.090
<b>General Mood</b>	.122	-.191
<b>Breathing problems</b>	-.042	.068
<b>Hands behaviour</b>	-.001	-.056
<b>Repetitive Face movements</b>	-.125	.074
<b>Body rocking and Expressionless face</b>	-.026	-.038
<b>Night time behaviour</b>	-.004	-.089
<b>Fear/anxiety</b>	-.171	-.095
<b>Walking/standing</b>	-.072	-.103

**Appendix F – 3: Correlation coefficients Severity score and family scales (QRS, HADS anxiety, HADS depression)**

	<b>QRS</b>	<b>Anxiety</b>	<b>Depression</b>
<b>Severity score total</b>	-.035	.139	.044
<b>Sitting domain</b>	.022	.090	.058
<b>Walking domain</b>	-.034	.033	-.047
<b>Hand use domain</b>	-.095	.054	.109
<b>Speech domain</b>	.055	.055	.173
<b>Epilepsy</b>	.130	.132	-.029
<b>Scoliosis</b>	-.122	.172	-.001

**Appendix F – 4: Correlation coefficients Severity score and family scales (PGS and PAS)**

	<b>PGS</b>	<b>PAS</b>
<b>Severity score total</b>	.019	-.090
<b>Sitting domain</b>	.030	-.071
<b>Walking domain</b>	.011	.070
<b>Hand use domain</b>	.009	-.012
<b>Speech domain</b>	.196	-.119
<b>Epilepsy</b>	-.099	.102
<b>Scoliosis</b>	-.033	-.236*

\*p < .05

**Appendix F – 5: Correlation Coefficients Positive (PGS and PAS) and negative (QRS – S and HADS) scales.**

	<b>QRS</b>	<b>Anxiety</b>	<b>Depression</b>
<b>PGS</b>	.290	-.064	.192
<b>PAS</b>	-.342*	-.412**	-.589**

\*p < .01, \*\*p < .001

**Appendix F – 6: correlation coefficients: QRS – S, HADS, PGS and PAS and parental; perception of progression/regression of skills domains**

	<b>QRS – S</b>	<b>HADS Anxiety</b>	<b>HADS depression</b>	<b>PGS</b>	<b>PAS</b>
<b>Breathing abnormalities</b>	<b>-.138</b>	<b>-.145</b>	<b>.045</b>	<b>.124</b>	<b>-.027</b>
<b>Physical fitness/robustness</b>	<b>-.189</b>	<b>-.166</b>	<b>-.148</b>	<b>-.227*</b>	<b>.219*</b>
<b>Mobility/walking</b>	<b>-.301**</b>	<b>-.312**</b>	<b>-.320**</b>	<b>-.156</b>	<b>.264*</b>
<b>Communication</b>	<b>-.056</b>	<b>.039</b>	<b>.010</b>	<b>-.101</b>	<b>.088</b>
<b>Purposeful hands use</b>	<b>-.092</b>	<b>-.260*</b>	<b>-.213*</b>	<b>-.212*</b>	<b>.283**</b>
<b>Repetitive hand movements</b>	<b>-.048</b>	<b>-.082</b>	<b>-.167</b>	<b>-.169</b>	<b>.203</b>
<b>Body rocking</b>	<b>-.041</b>	<b>-.184</b>	<b>-.227*</b>	<b>.022</b>	<b>.094</b>
<b>Mood changes</b>	<b>-.229*</b>	<b>-.250*</b>	<b>-.202</b>	<b>-.217*</b>	<b>.223*</b>
<b>Problems with anxiety</b>	<b>-.363**</b>	<b>-.335**</b>	<b>-.301**</b>	<b>-.181</b>	<b>.323**</b>
<b>Night-time behaviour</b>	<b>-.109</b>	<b>.089</b>	<b>.087</b>	<b>-.016</b>	<b>-.022</b>
<b>Feeding problems</b>	<b>-.142</b>	<b>.020</b>	<b>.054</b>	<b>.075</b>	<b>-.037</b>

\* P< .05, \*\*p< .005

**APPENDIX G**  
**LONGITUDINAL DATA NORMALITY TESTS AND HISTOGRAMS**

## Appendix G – 1: Activity Questionnaire (AQ) normality tests

Table G – 1.1: Activity Questionnaire (AQ) normality tests

	Kolmogorov-Smirnov (df)	Asymp. Sig. (2-tailed)	Shapiro-Wilk (df)	Asymp. Sig. (2-tailed)
AQ Total score All participants	.196 (50)	.000	.914 (50)	.001
AQ Overactivity	.135 (50)	.023	.918 (50)	.000
AQ Impulsivity (Mobile)	.202 (24)	.013	.909 (24)	.033
AQ Impulsivity (Immobile)	.340 (26)	.000	.753 (26)	.000
AQ Impulsivity (All participants)	.178 (48)	.001	.839 (48)	.000

Figure G – 1.1 Histogram with normality curve for the AQ Total score (All participants)

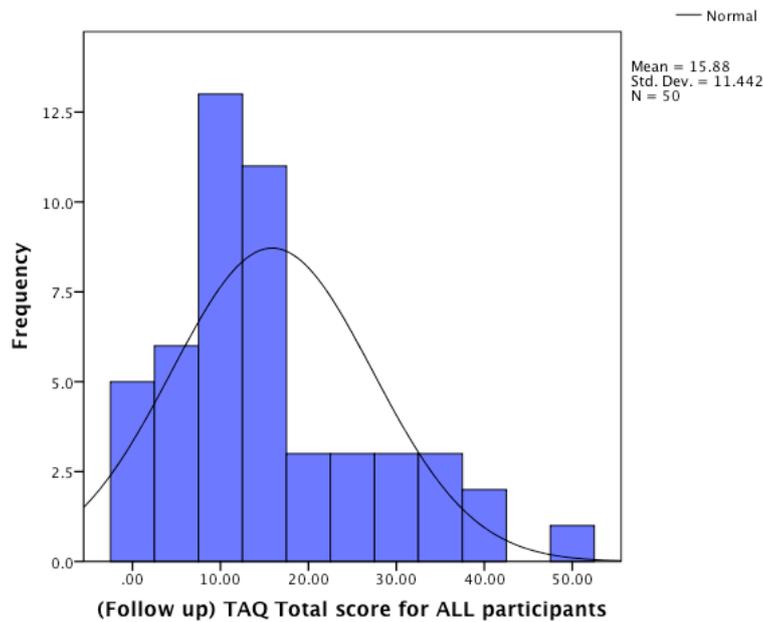


Figure G – 1.2 Histogram with normality curve for the AQ Overactivity subscale

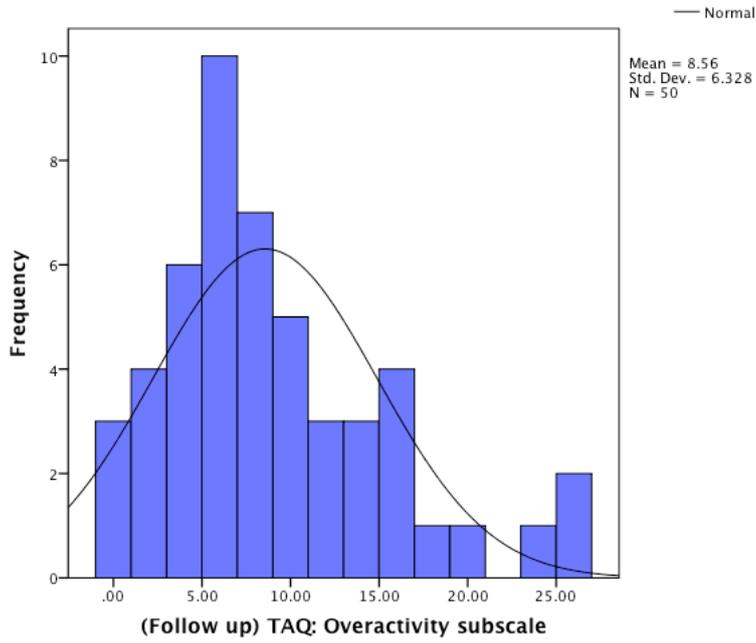


Figure G – 1.3 Histogram with normality curve for the AQ Impulsivity subscale (Mobile)

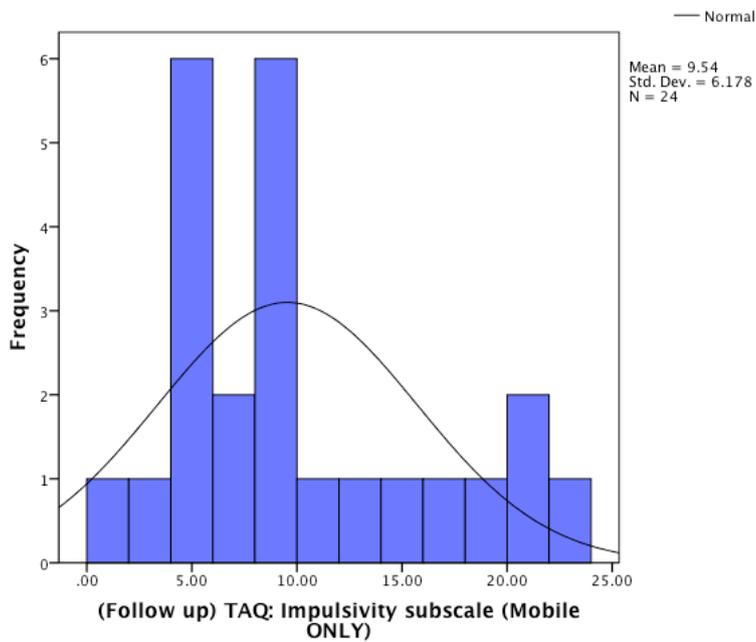


Figure G – 1.4 Histogram with normality curve for the AQ Impulsivity subscale (Immobile)

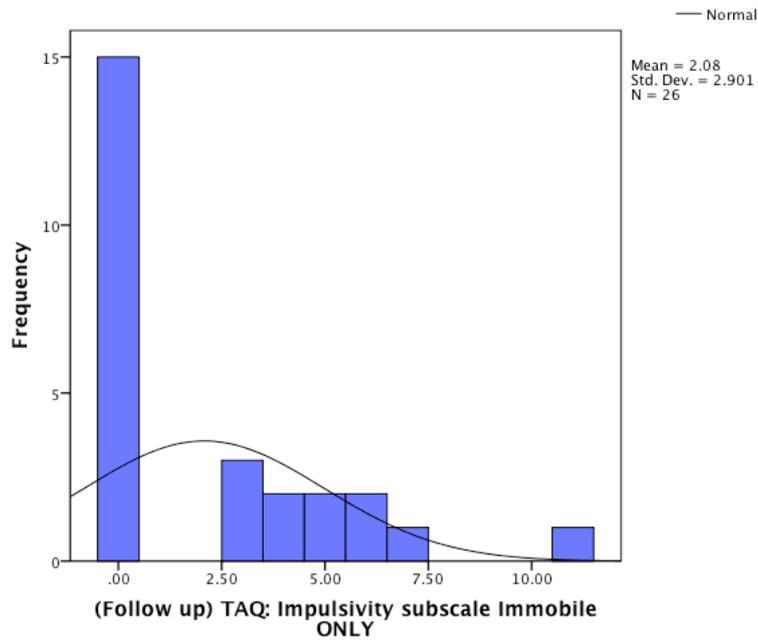
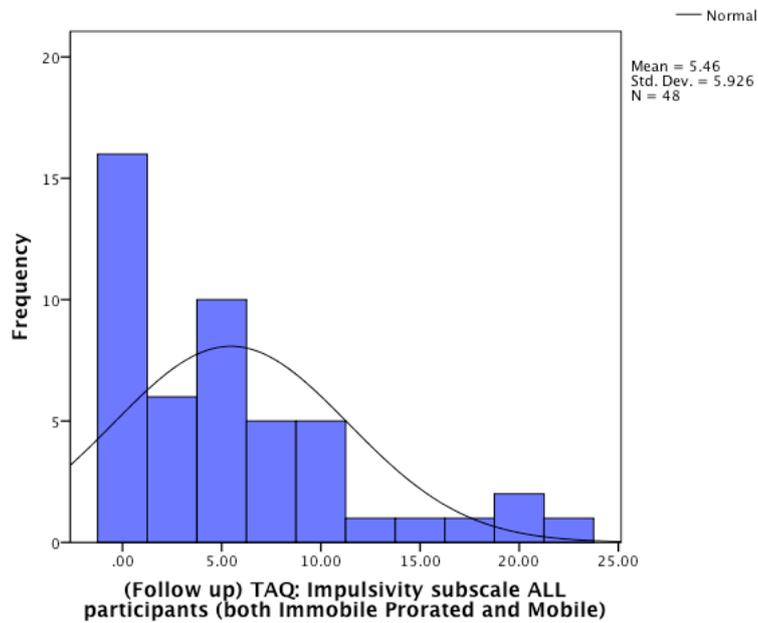


Figure G – 1.5 Histogram with normality curve for the AQ Impulsivity subscale (All participants)



## Appendix G – 2: Mood, Interest and Pleasure Questionnaire Normality tests

Table G – 2.1: Mood, Interest and Pleasure Questionnaire (MIPQ – S) Normality tests

	Kolmogorov-Smirnov (df)	Asymp. Sig. (2-tailed)	Shapiro-Wilk (df)	Asymp. Sig. (2-tailed)
MIPQ Total score	.115 (49)	.108	.973	.326
MIPQ: Mood subscale	.191 (49)	.000	.899	.001
MIPQ: interest and Pleasure subscale	.131 (49)	.036	.947	.029

Figure G – 2.1: Histogram with normality curve for the MIPQ – S Total score

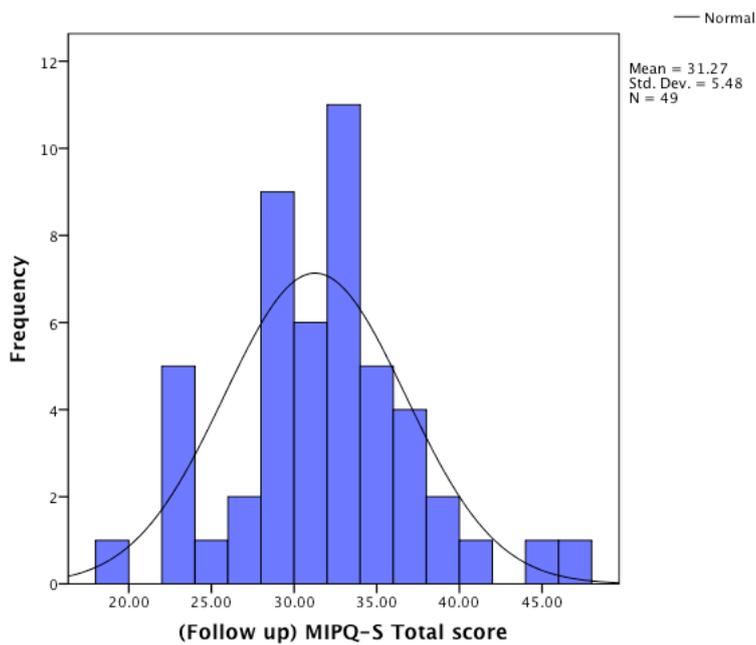


Figure G – 2.2: Histogram with normality curve for the MIPQ – S Mood subscale

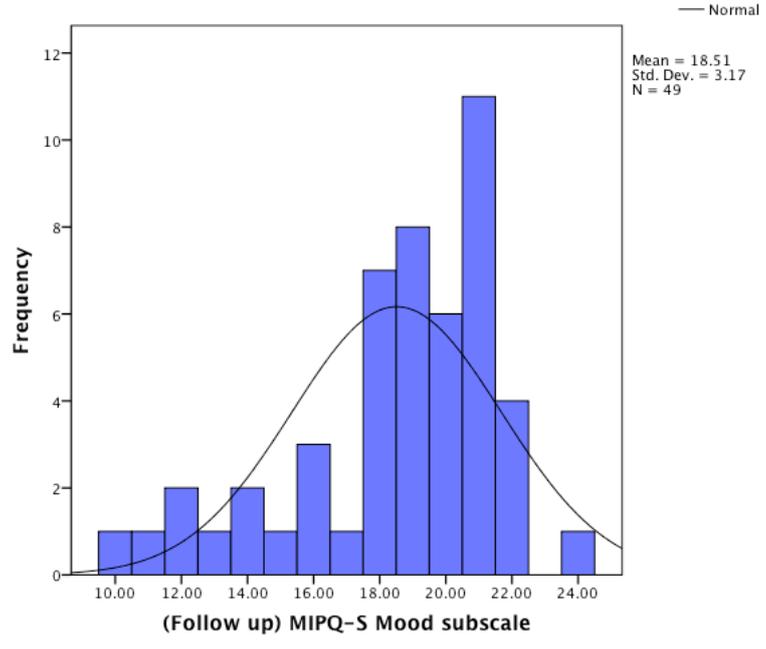
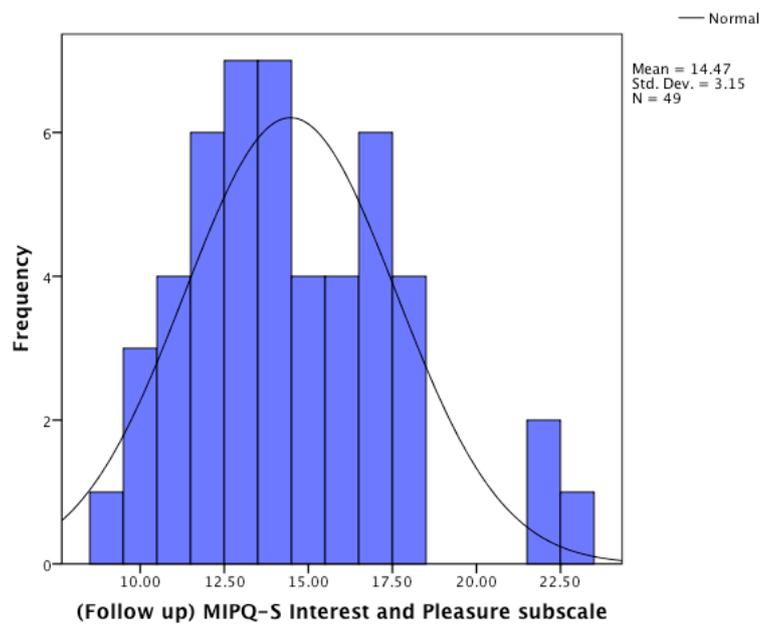


Figure G – 2.3: Histogram with normality curve for the MIPQ – S Interest and Pleasure subscale



**Appendix G – 3: Rett Syndrome Behavioural Questionnaire (RSBQ) Normality tests**

Table G – 3: Rett Syndrome Behaviour Questionnaire (RSBQ) Normality Tests

	<b>Kolmogorov-Smirnov (df)</b>	<b>Asymp. Sig. (2-tailed)</b>	<b>Shapiro-Wilk (df)</b>	<b>Asymp. Sig. (2-tailed)</b>
RSBQ Total	.077 (49)	.200	.974 (49)	.354
RSBQ General Mood	.150 (49)	.008	.936 (49)	.010
RSBQ Breathing Problems	.132 (49)	.033	.950 (49)	.036
RSBQ Hands Behaviour	.191 (49)	.000	.920 (49)	.003
RSBQ Repetitive face movements	.137 (49)	.023	.923 (49)	.003
RSBQ Body Rocking and expressionless face	.147 (49)	.010	.933 (49)	.008
RSBQ Night-Time behaviour	.209 (49)	.000	.861 (49)	.000
Fear and Anxiety	.102 (49)	.200*	.951 (49)	.042
Walking and standing	.293 (49)	.000	.800 (49)	.000

Figure G – 3.1: Histogram with normality curve for RSBQ Total score

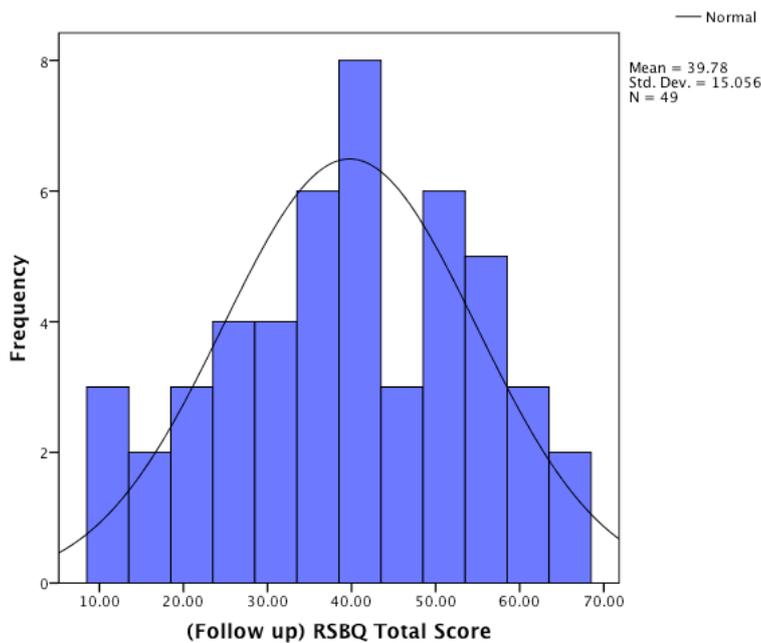


Figure G – 3.2: Histogram with normality curve for RSBQ General Mood domain

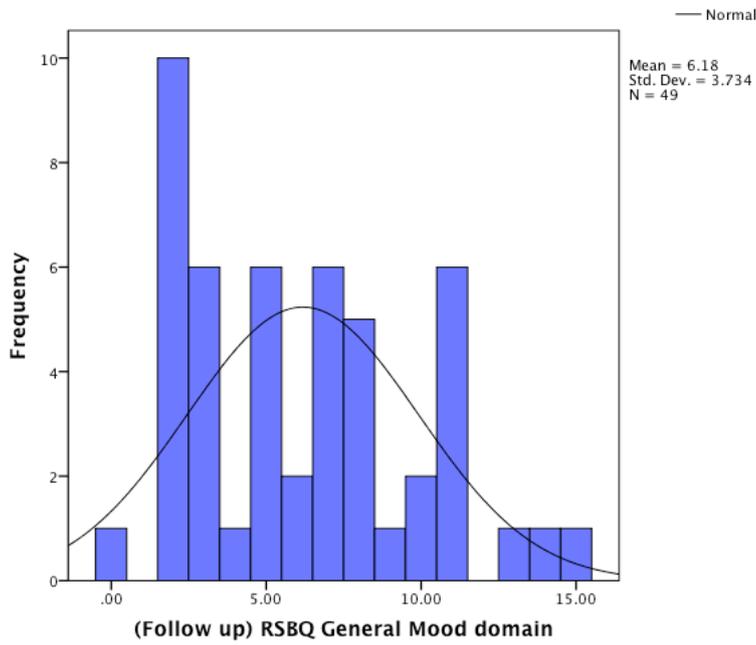


Figure G – 3.3: Histogram with normality curve for RSBQ Breathing abnormality domain

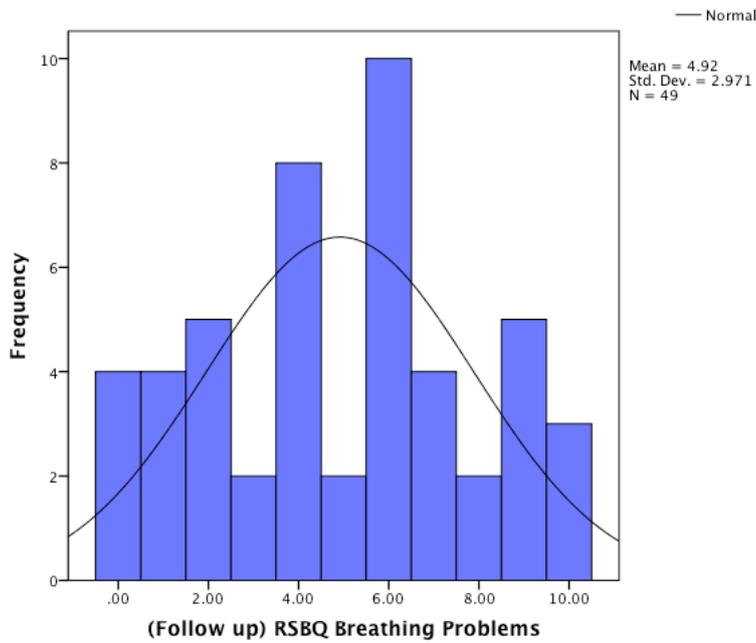


Figure G – 3.4: Histogram with normality curve for RSBQ Hand behaviour domain

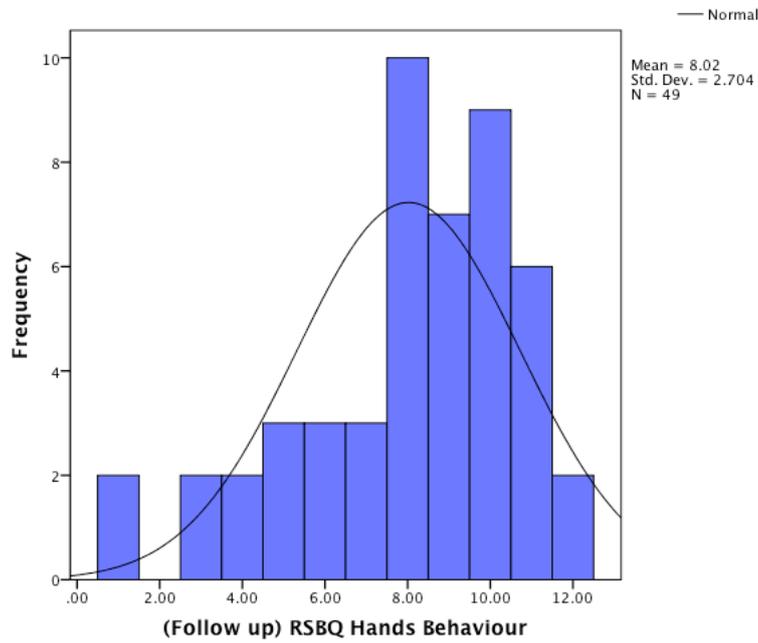


Figure G – 3.5: Histogram with normality curve for RSBQ Repetitive face movement domain

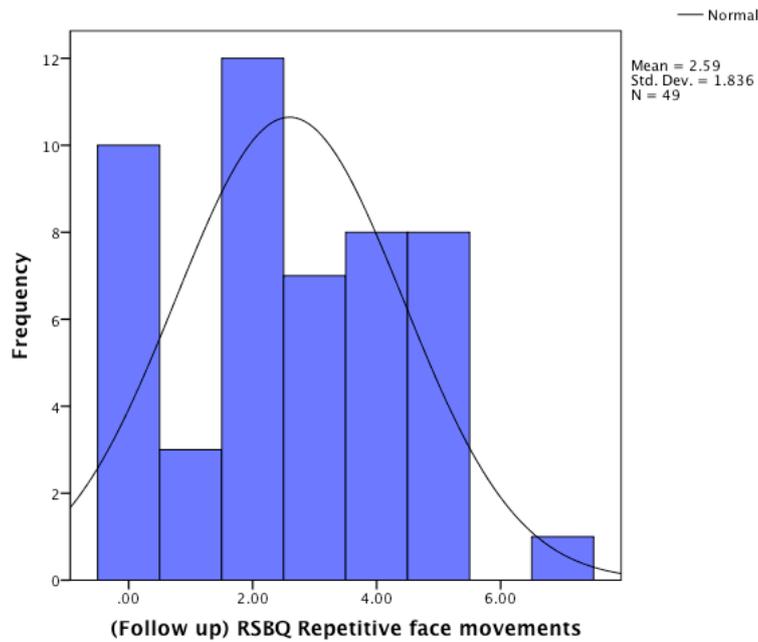


Figure G – 3.6: Histogram with normality curve for RSBQ Body rocking and Expressionless face domain

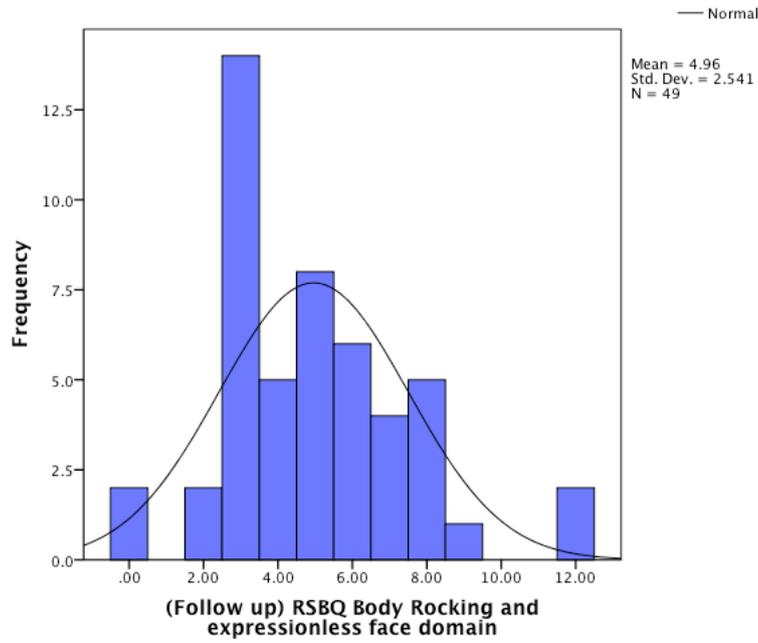


Figure G – 3.6: Histogram with normality curve for RSBQ Night-Time behaviour Domain

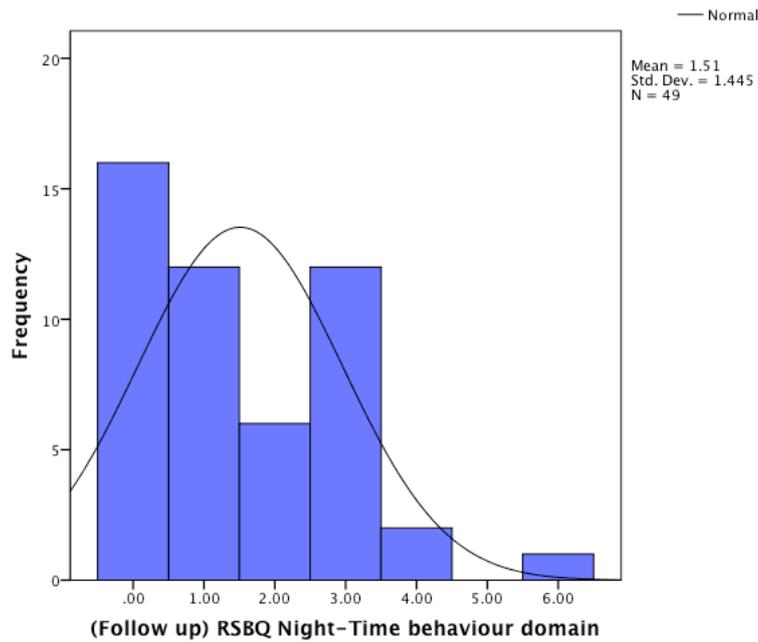


Figure G – 3.7: Histogram with normality curve for RSBQ Fear and Anxiety domain

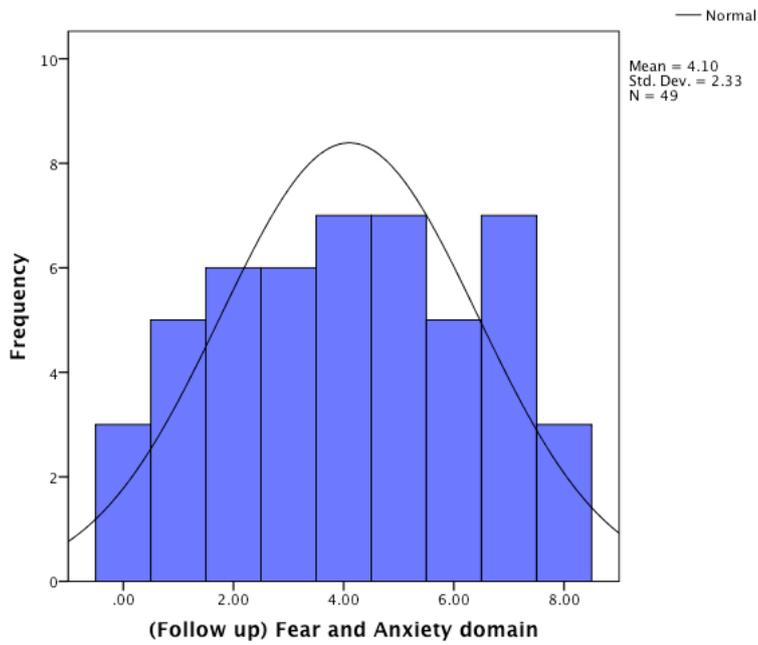
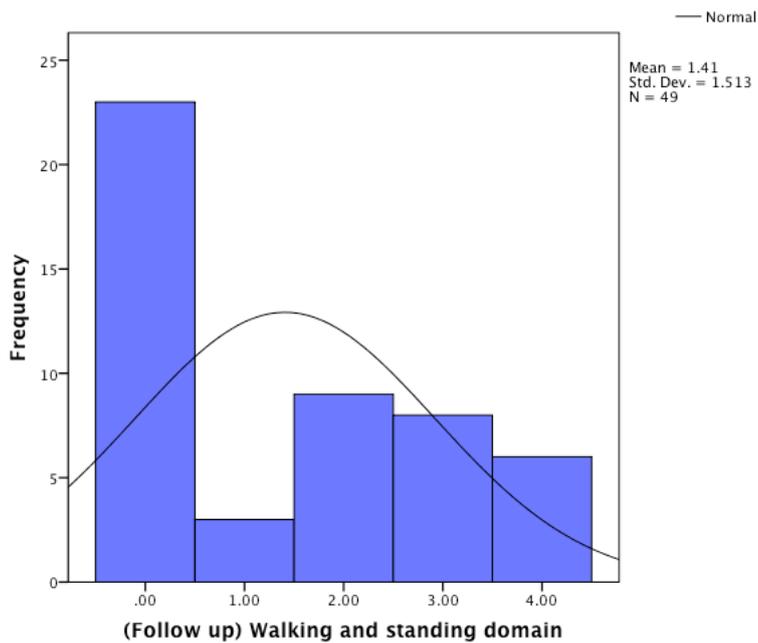


Figure G – 3.8: Histogram with normality curve for RSBQ Walking and standing domain



### Appendix G – 4: Family Measures Normality tests

Table G – 4: Questionnaire on Resources and Stress Short Form (QRS – F), Hospital Anxiety and Depression scale (HADS), Positive Gains Scale (PGS) and Positive Affective Scale (PAS) Normality tests

	Kolmogorov-Smirnov (df)	Asymp. Sig. (2-tailed)	Shapiro-Wilk (df)	Asymp. Sig. (2-tailed)
QRS –F	.159 (50)	.003	.955 (50)	.057
HADS Anxiety	.113 (49)	.158	.960 (49)	.096
HADS Depression	.163 (49)	.002	.912 (49)	.001
PGS	.135 (49)	.026	.895 (49)	.000
PAS	.123 (49)	.060	.956 (49)	.065

Figure G - 4.1: Histogram with normality curve for QRS – F

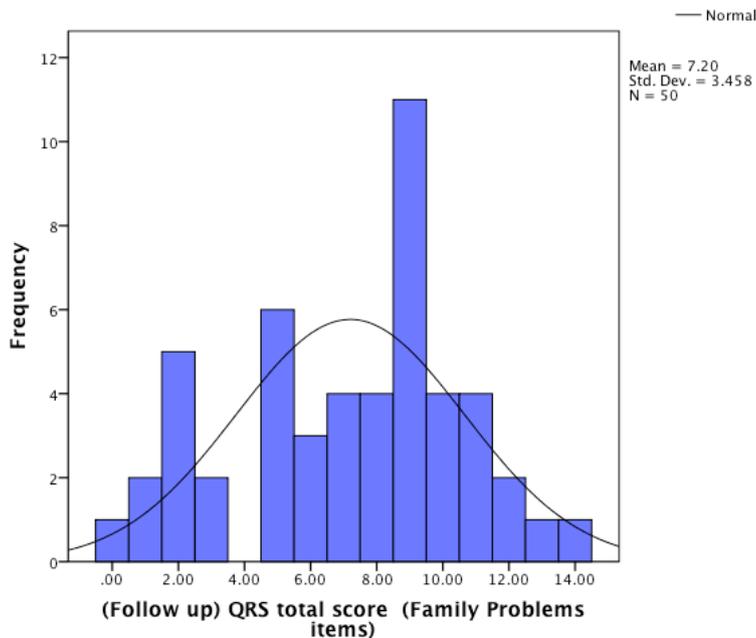


Figure G – 4.2: Histogram with normality curve for HADS Anxiety subscale

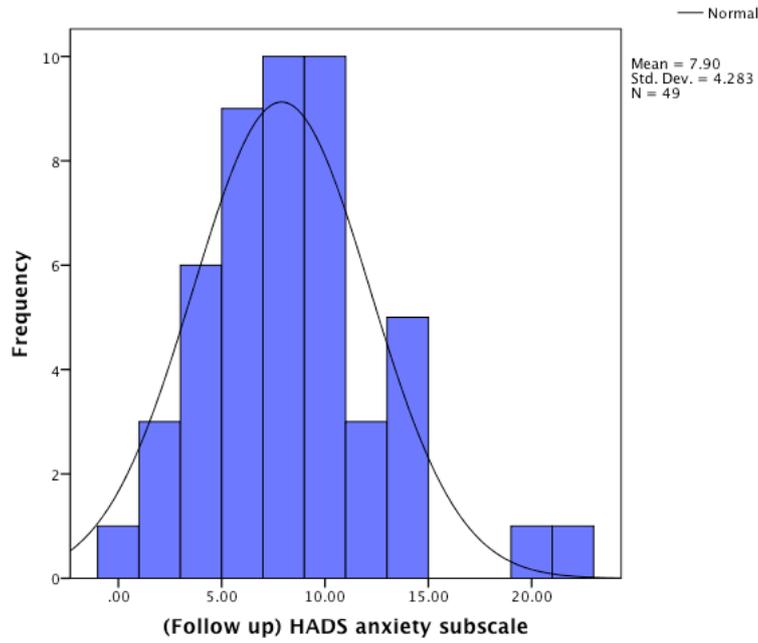


Figure G – 4.3: Histogram with normality curve for HADS Depression

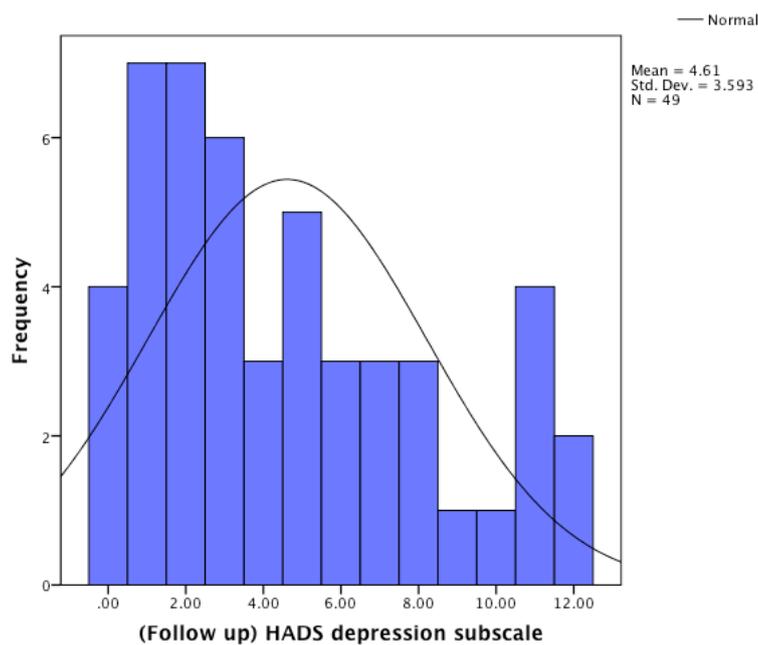


Figure G – 4.4: Histogram with normality curve for PGS

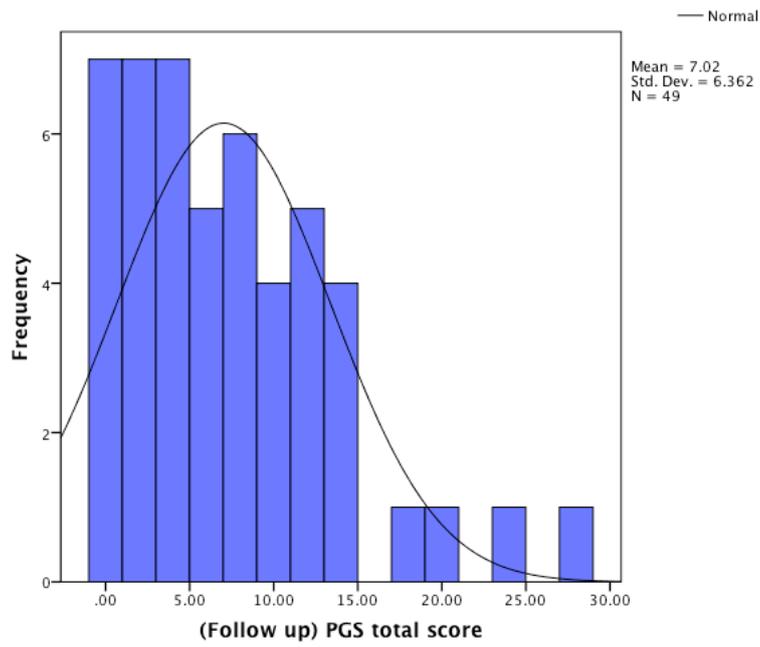


Figure G – 4.5: Histogram with normality curve for PAS

