A systematic review of non-medical interventions in Rett Syndrome and a research study into attenuated behaviours in Rett Syndrome

A Thesis Submitted to Cardiff University of the Degree of Doctor of Clinical Psychology

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Abstract

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This thesis was submitted in May 2018 for the partial fulfilment of the award of Doctor in Clinical Psychology (DClinPsy) at Cardiff University. The thesis investigated a review of non-medical interventions in Rett Syndrome and the prevalence of attenuated behaviours in Rett Syndrome. Rett Syndrome is a rare neurodevelopmental genetic disorder which is characterised by period of outwardly typical development followed by a period of regression around 12-18 months. The regression is causes progressive disabilities in speech, motor and hand use. Physical comorbidities are often present including breathing difficulties, the requirement of feeding tubes, anxiety, gastrointestinal difficulties and orthopaedic issues. The condition is almost exclusive to females. Despite the inability to use their body to communicate, research has shown that individuals with Rett Syndrome are more intellectually capable than their body allows them to present.

Paper 1 describes a systematic review of non-medical interventions researched into Rett Syndrome. The electronic databases were searched (Embase, PsychINFO and MEDLINE). Thirteen papers which met the quality rating threshold were reviewed and the methodology was assessed. Communication interventions were the most researched intervention. Alternative interventions included fitness and brainstem activation. Eleven of the studies described positive results. Recommendations for clinical practice and future research are made.

Paper 2 describes an empirical study investigating the prevalence of attenuated behaviours [Autistic Catatonia] in Rett Syndrome and its presence during 'Rett Episodes'. Parents of 28 individuals with Rett Syndrome completed questionnaires relating to attenuated behaviours and Rett Episodes. The findings revealed the presence of attenuated behaviour in individuals with Rett Episodes but this was not specific to Rett Episodes. The severity of attenuated behaviour was negatively correlated with age. Recommendations for clinical implications and further research are made.

Paper 3 discusses an evaluation of the research process. The paper critically appraises the research across both papers including the strengths and limitations. The paper includes key reflections and process information that was not permitted within the constraints of the author guidelines for submission.

Declaration

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

Signed …… (candidate) Date ……

STATEMENT 1

This thesis is being submitted in partial fulfillment of the requirements for the degree of DClin Psych

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STATEMENT 2

This thesis is the result of my own independent work/investigation, except where otherwise stated.

Other sources are acknowledged by explicit references. The views expressed are my own.

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Finally, I would like to thank all my family for their support. Completing the course alongside my children's early years has at times been tough and challenging to balance. However, their smiles and cuddles have made it all possible.

Paper 1

Non-medical interventions for individuals with Rett Syndrome: A systematic review

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Prepared in accordance with author guidelines of Journal of Applied Research of Intellectual Disabilities (Appendix 1). This journal follows American Psychological Association reference style.

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Abstract:

Background: Research into Rett Syndrome has included various medical interventions. However non-medical interventions are relatively under researched due to the challenges of small samples sizes. Recent technological communication intervention advances have contributed to the evidence base of non-medical interventions in Rett Syndrome.

Method: The Embase, PsychINFO and MEDLINE were systematically searched for peer reviewed papers describing non-medical interventions for Rett Syndrome. All identified papers were evaluated for methodological quality.

Results: The systematic review identified twenty-two studies, including case studies and case series, thirteen of which were deemed to be of adequate methodological quality and reported on a total of N=60 participants (59=female / 1=male). The interventions were primarily communication interventions in the form of music, assistive technology, augmentative and alternative communication strategies, attentional training and cognitive rehabilitation training. Other interventions targeted fitness and brainstem activation. All studies reported some positive outcomes, however such improvements were not consistently attained or documented and methodological flaws and/or small N samples were common.

Conclusions: The current review highlights the paucity of high-quality research on non-medical interventions for Rett Syndrome. Future research is needed to build on current research and to improve the validity and generalisability of interventions.

Keywords: Rett Syndrome, Non-medical interventions, Systematic Review

Introduction

Rett Syndrome (RTT) is a rare neurodevelopmental disorder occurring in one in every 10,000 live births. It is almost exclusive to females and results in severe to profound cognitive and physical impairments. Diagnosis is made clinically, but typically individuals have a mutation in the methyl-CpG binding protein-2 (MECP2) gene (Amir et al., 1999). Classic RTT symptoms follow an outwardly typical period of normal development. However recent research proposes that early development may be compromised (Einspieler, Freilinger, & Marschik, 2016; Leonard & Bower, 1998; Marschik et al., 2013). Affected individuals follow a four stage trajectory, starting between six and eighteen months (Hagberg, 2002; Hagberg, Aicardi, Dias, & Ramos, 1983; Hagberg, Witt-Engerström, Opitz, & Reynolds, 1986; Neul et al., 2010; Witt Engerstrom, 1990). Initially individuals experience a period of stagnant psychomotor development (stage one) followed by a period of regression between the age of 1 and 4 years (stage two). Regression consists of loss of previously acquired purposeful hand skills, gait abnormalities and the emergence of hand stereotypes' including hand wringing, clapping and tapping (Neul et al., 2010). The regression period further includes impaired communication and social withdrawal. Stage three consists of a period of stagnation before motor deterioration (stage four) which can occur years later. This progressive deterioration will eventually result in individuals being unable to walk, talk and use their hands functionally (Sigafoos et al., 2009).

Individuals commonly experience associated comorbidities, including epileptic seizures, impaired sleep, growth impedance and periods of incongruous laughing / screaming (Cass et al., 2003; Cianfaglione, Hastings, Felce, Clarke, & Kerr, 2015; Neul et al., 2010; Reilly & Cass, 2001; Young et al., 2007). In addition, individuals with RTT experience autonomic abnormalities in the form of breath holding, hyperventilation and abdominal bloating (Mackay

et al., 2017). Three quarters of women survive by 25 years (Laurvick et al., 2006). RTT is currently incurable.

Research into RTT has primarily focused on addressing the phenotypic impairment and medical interventions. Despite the life-long challenges individuals with RTT experience, to date there has been only limited research into non-medical interventions. Sigafoos et al (2009) highlight the challenge in ranking intervention goals, given the range of impairments and the profound nature of them. Researching communication skills interventions is thought to be imperative given the nature of speech loss and restricted communicational abilities (Sigafoos et al., 2009). A systematic review into communication interventions in RTT (Sigafoos et al., 2009) concluded that the paucity of research in the area was impeding development of evidenced-based practice and that the extant research was of poor quality. Sigafoos et al. (2009) proposed suggestions for improvements in experimental design, including the need for pre-intervention assessments, follow up, generalizability, reliability and procedural data. Since their review there have been developments in the use of assistive technology with RTT syndrome.

A systematic review into assistive technology (any item, piece of equipment, software program, or product system that is used to increase, maintain, or improve the functional capabilities of persons with disabilities in individuals) with intellectual disabilities (Perelmutter, McGregor, & Gordon, 2017) found it to be a helpful resource, however the participants within these research studies did not present with the profound cognitive and physical impairments associated with RTT. Longitudinal research into eye gaze assistive technology in individuals with profound physical and communication impairments, found improvements in eye gaze ability in order to communicate effectively given practice and longevity of interventions (Borgestig, Sandqvist, Parsons, Falkmer, & Hemmingsson, 2016). The use of augmentative and

alternative communication (AAC) strategies have been proposed as pivotal for individuals with RTT (Sigafoos et al., 2009, 2011). Research into the use of AAC strategies such as picture exchange communication system's (PECS) and vocal output communication aid's (VOCA) in individuals with an intellectual disability have been positive (Lancioni et al. 2008; Lancioni et al. 2008). Recent research into RTT has introduced the use high technology AAC systems such as eye gaze technology to assist in the development of broader, more complex communication skills (Simacek, Reichle, & McComas, 2016).

Study Rationale

Sigafoos et al. (2009) indicated that despite positive outcomes for 84% of the participants, the evidence for the use of communication interventions in RTT remains inconclusive. Furthermore, the 2009 review was limited to communication interventions. The recent developments in assistive technology and AAC interventions technology has not been systematically reviewed in the RTT population. Therefore, the current review aimed to systematically review the quality and efficacy of all non-medical interventions that have been used in Rett Syndrome.

Method

The current systematic review methodology was based on Higgins & Green (2001) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed (Moher et al. 2009).

Search Strategy

Embase (1980-), PsychINFO (1806-) and MEDLINE (1980) electronic databases were searched by the first author (AA). Given the limited literature on Rett Syndrome interventions, no date restrictions were applied but the search was limited to papers published in English. The following search string was used: 'Rett Syndrome' AND 'Interventions'. The references of all initially identified were subsequently hand searched for additional studies. In addition, Sigafoos et al (2009) references was searched to identify related studies. The search sought to identify papers where search terms appeared in the title, abstract or keywords.

Inclusion and exclusion criteria

The review was limited to peer reviewed articles and so-called 'grey literature' (dissertations, conference abstracts and letters to the editor) was excluded. Studies were included if they were primarily about non-medical interventions for RTT and papers reporting pharmacological and other medical interventions were excluded. The author chose to exclude medical interventions, firstly due to the range of potential medical interventions for RTT which might be outside the authors' area of expertise. Secondly, it was felt that non-medical interventions were largely under-represented within the literature and therefore a review of the literature would allow for an increased profile of the importance of non-medical interventions

The search terms used were intended to have a high sensitivity and low specificity so as to capture a wide range of potential interventions from a variety of disciplines which might use differing or unfamiliar terminology that may have otherwise been missed. The initial search scope was manageable (n353); if this was a significantly larger number the search terms would have been amended to balance the sensitivity and specificity more efficiently.

Search Results

The abstracts were downloaded to a reference manager. Titles and abstracts were screened and relevant full texts were downloaded. The initial search yield N=353 papers, which were reviewed by the first author (AA) using the inclusion and exclusion criteria. This resulted in N=333 papers being rejected on the grounds that they were duplicates, conference papers, phenotype studies, review studies, systematic reviews, pharmacological or medical intervention or assessment studies. The reference sections of each paper were screened for additional papers, which yield an additional two additional papers were identified and included in the review. An independent researcher replicated this process and any discrepancies around eligibility were discussed and resolved. A total of N=22 papers were included in the final review. Fig. 1 summarises the PRISMA search process (Moher D et al., 2009).

Figure 1 here

The lack of randomised control trials and the heterogeneity of the studies did not allow for a meta-analysis (Centre for Reviews and Dissemination, 2009).

Data extraction

Sample data including year of publication, participant characteristics, current functioning, and setting were extracted (Table 1). Study characteristics were also extracted including target behaviour and variables, research design, formal measures, intervention and results (Table 2).

Table 1 and Table 2 here

Quality Measure

The Quality Appraisal Tool for Case Series [QATCS] (Moga, Guo, & Harstall, 2012) was used as recommended by Zeng et al (2015) and is a 20 item tool specifically developed for case series for a variety of interventions, with each item being scored as Yes, No, Unclear or Partial. Whilst it does not provide for numeric scoring, recent systematic reviews have assigned one point for Yes and half a point for Unclear or Partial responses (Auger, Hernando, & Galmiche, 2017; Roland, Skillington, & Ogden, 2017). In its original form, studies with a score above 14 are deemed to be methodologically adequate (Auger et al., 2017). The QATCS is designed to be tailored to specific reviews (Guo, Moga, Harstall, & Schopflocher, 2016) and was modified for the current review with the omission of items 3-4,7,9 & 16. Thus, each study in the current review was scored 0-15 and following Auger et al (2017)'s criteria, a score of nine or above more was deemed to reflect acceptable methodological quality.

Inter-rater reliability

The article selection stage required removing duplicates, grey literature and medical interventions. This stage of selection did not involve differential opinions or judgements there it was not deemed necessary to conduct inter-rating reliability at this stage.

Data quality was initially scored by the first author (AA). After this a second reviewer independently assessed 20 % of the papers studies against the criteria. A Kappa of .56 was attained, indicating a moderate level of reliability (Altman, 1991). All the raters scores fell within the same cut off scores. Any disagreements were resolved via discussion.

Results

Quality ratings and exclusions

Of the studies reviewed, 13/22 scored as being acceptable quality. Quality ratings ranged from 3.5-11 (mean= 9), with a possible association between the year of publication and quality rating. Furthermore the types of interventions used appeared to change over time. For example, earlier interventions had a tendency to focus on physical mobility restriction such as repetitive hand movements via the use of hand splints and restraint (1, 2, & 4). Whereas more recent interventions have focused on increasing the brevity of individuals communication ability. Lower quality papers failed to report a clear hypothesis, objective or aims (1,4,6 & 8), lack of clear intervention description (3, 4, 6 & 13), a priori outcome measures (1, 3 & 8) and lack of follow up data (2,3,6 & 8). Both the high and low quality papers would have benefitted from improved clarity of their eligibility criteria, statements of blindness of researchers, estimates of random variability, adverse events disclosure and competing sources of interest statements.

Characteristics of studies

Participants

The number of participants in each study ranged from 1-21 (mean = 4.6) and represented N= 60 participants in total. Ten of the studies reported on from 1- 4 participants (7,9 & 15-22) who were either recruited via existing cohorts or via non-specified recruitment methods. The study with the largest participant number (N=21 Study 11) was recruited via the Swedish National Rett Centre. The second largest participant number study (N=12 Study 12) was recruited via the Italian Rett Association.

All study participants had a diagnosis of RTT and all but one participant were females (11). One study (22) included two further participants with Autism Spectrum Disorder (the results of which were excluded from this review). Authors specified specific ages for participants in ten of the thirteen studies. The remaining three studies only specified age ranges across participants (Studies 9, 11 & 12). The participant ages ranged from 3-44 years. There was variability in the reporting of functioning and stage of RTT, with the latter only reported in four studies, namely 7, 9 & 12 (stage III) and 15 (stage IV). Participants were reported to be severe to profound intellectually disabled (5, 12, 16, 18 & 20) and/or with no functional speech (5, 7, 12, 15, 16 & 18-21).

Target behaviours

Out of the thirteen papers, eleven broadly related to communication interventions (5 7, 12 & 15-22). The remaining papers targeted physical fitness (Study 9) and brainstem activity (11).

Of the communication interventions, eight studies specifically targeted either learning of a new communication skill via symbols, words, labels and mircoswitches or using communication aids to make choices and requests (5, 7, 12, 16 & 18-22). Other target behaviours were frequency of hand use and turn taking (17) and increase in attention span (12).

Seven studies measured secondary dependent variables alongside the main target variables (5, 9, 12, 16, 18-20). These included increase of parental awareness of child's communication modes (7), functional motor improvements (9), adaptive behaviours (12), dependence on help from others (12) happiness (16 & 19), mood (18, 20) and adaptive responses (20). Target behaviour of the RTT phenotype 'hand stereotypes' were measured as a secondary variable in four studies (12, 16 18 & 20).

Intervention procedures

In the studies that reported on communication procedures, eight included the use of assistive technology or AAC interventions (5, 7, 16 & 18-22). Interventions included the use of assistive technologies such as storybook (5), micro switch (16 & 19), PECS and VOCA (18) and sensors and a personal computer (20). Interventions using AAC included computer based ACC system requiring learning of choices of a picture symbol or eye gaze and head / nose movements (7), use of a speech generated device using eye gaze or touch (21) and micro switch responses (22).

Further communication interventions used music therapy (11 & 17), attentional training (12) and cognitive rehabilitation training (15). The physical exercise study (9) included a treadmill programme.

Study design

Of the thirteen studies, six used a multiple baseline design (5 & 21) or multiple-probe design (7 16, 20 & 22). Two studies used pre-test / post-test design (9 & 12). Other experimental designs included controlled within-subject study design (11), ABAB design (19) and alternative single case research designs (15 & 17-18).

Types of outcome measure

The majority of the studies used individualised frequency measures to measure target behaviours via the use of analysing video or in session recordings (5, 7, 12 & 15-22). Three studies used objective measures of indices of happiness (16, 18 & 20). Two studies measured autonomic nervous system signals including pulse (9) and EEG activity (11). One study additionally used a standardised measure of adaptive behaviour (12). Whilst the majority of the studies included inter-rater reliability scoring across the measures, the results may be vulnerable to biases from the coders, who were affiliated with the study.

Outcomes

Table 2 shows the specific outcomes for each study. Of the thirteen studies, results were found to be solely positive on the target behaviours in eleven of the studies (5, 7, 9, 11-12

&15-20). In study 21, the results were mixed for the participants. The results of study 22, noted that the target behaviour was achieved (learning), however retention of the target behaviour was not achieved. None of the studies reported adverse effects or reported a decrease in target skills or ability.

Common Methodological Issues

It was not possible to assess the representativeness of the sampling frames as most studies did not report on the recruitment sampling in adequate detail (5, 7, 9, 16, 17, 19 & 20). Similarly, it was not possible to comment on the potential for selection or response bias. The potential for biases was rarely reported and it was noted that the earlier studies were often reported in narrative form and hence more susceptible to bias. In addition, most studies did not report information regarding other interventions that could have been delivered in parallel, which creates difficulties with respect to identifying potential confounding variables and assessing the validity of the results. In the studies that were conducted over a substantial length of time to facilitate learning, potential confounding factors such as maturation and relational variables were not reported.

Discussion

This is the first systematic review of non-medical interventions for RTT, following on from an earlier review of communication-based interventions in RTT (Sigafoos et al., 2009). Earlier studies tended to be of low methodological quality and focussed on physical interventions and communication which may reflect recent changes in the types of interventions used in RTT (e.g the move from using restraints). Of the thirteen studies included in the review, most

focused on communication as the primary target intervention. In eleven of the studies individuals with RTT showed improvement in the target behaviour and secondary targets (such as happiness or stereotypes), suggesting that such individually tailored interventions can be of benefit to individuals with RTT. The interventions found cognitive abilities such as attention and read-writing can be increased and sustained using well-structured individualised intervention programmes such as attentional training and cognitive rehabilitation training (12, 15 & 16). In addition, global abilities or quality of life can also improve (12, 15, 16, 18-19). The use of technology such as micro-switch (16 & 19), PECS and VOCA (18) and other forms of assistive technology (7, 20-22) can facilitate improved communicational abilities. The implementation of communication interventions was found to reduce stereotyped behaviours (16, 18 & 20). In addition, the current review found the use of a music therapy intervention assists the development of intentional communication (17). In addition, parents can be trained to assist their child in initial communication skills and learn to interpret unconventional non-verbal communication signals (5). The review found there to be a strong evidence for communication interventions, however such interventions are resource intense and usually of relatively high cost. Historically, computer-based assistive technology has had both high initial costs and the ongoing costs of updating the software but the recent development of mobile devices and associated app technology may significantly reduce these costs. Individuals with less existing communicative ability (e.g no vocalisations, or communicative hand movements) would benefit the most from 'higher technology' assistive technology interventions which assist in the use of communication modes such as eye gaze technology.

As well as communication outcomes, physical fitness can also be improved using a low intensity treadmill programme (9). In addition, in support of anecdotal evidence of music

therapy, different musical stimuli can evoke different sympathetic and parasympathetic responses in individuals with RTT (11).

Limitations

Given the wide-ranging and profound nature of both physical and communication abilities individuals with RTT encounter and the age and stage of RTT, the high quality and effective interventions were largely tailored specifically to the individuals. Therefore the studies were disparate from each other in terms of using similar measures, experimental conditions and interventions. It is challenging to draw firm conclusions regarding the interventions collectively. Furthermore, the rarity of RTT leads to challenges in recruitment and most reported studies are N=1 or small N designs. This compromises the possibility of undertaking more sophisticated controlled studies or trials. Given most of the studies have severe limitations in their external validity and generalisability to wider RTT populations and as such, results should be interpreted cautiously. Future research will be needed to establish the efficacy of the interventions within RTT.

A further limitation was that many of the studies in the current review did not report on the progressive nature of RTT. Depending on the RTT stage, a decline in functioning or some degree of recovery may be expected. In those studies that did specify RTT stage and age, there was no consideration of the implications of this with regard to the target outcome and the potential for it to be a confound variable. Similarly, there was only limited reporting of co-morbid medical issues and / or concurrent pharmacological interventions. The potential interaction between biological / medical interventions and environmental interventions is an area that may require further exploration.

Recommendations for clinical practice

The main aspect of the individual studies is to tailor specific clinical interventions according to the individual. An assessment of the skills they currently hold will inform the starting point of the intervention and then interventions can be built on depending on the outcome. For example, some individuals will be able to use micro switches using their motor abilities, whilst other individuals will be limited to eye gaze technologies. Similarly, assessment and outcome measures, are best tailored to the individual. Additional measures, measuring secondary outcomes will assist in the review of the efficacy of the interventions.

In terms of the choice of interventions, the recent advances in technology offer promising contributions to assisting unconventional communication strategies in the absence of traditional communication strategies. However these resources will be inevitably more resource intensive and expensive. Improving access to assistive technology (both low and high technology), environmental stimuli and engagement should assist in improving communication, mood and quality of life outcomes for individuals with RTT. 'Low tech' solutions such as PECS and VOCA should be considered when motor abilities permit, to allow for increased access with minimum financial constraints. Whereas 'high tech' approaches such as speech generated devices, micro switch and eye gaze technology are more appropriate if the person's intellectual and motor abilities are profound (Matson, 2012).

Interventions should be formulated with parental support wherever and assist in upskilling the parents in recognising communication attempts in their child. Once trained, parents can complete this alongside the existing care of their child.

Research into physical fitness in RTT highlighted the low baseline of fitness for individuals with developmental disabilities. In light of the research, physical fitness should be incorporated into care planning of individuals with RTT to improve their baseline mobility and fitness. In typical clinical settings individuals will already be being offered a range of support from a variety of differing disciplines. It is imperative that practice based evidence is encouraged, shared and attempts are made to researching practice based evidence to inform the evidence base.

Recommendations for Clinical Psychologists

The review highlights the need for increased accuracy of assessments of cognition, an area of which Clinical Psychology can lead on developing. Within a training and consultancy model, Clinical Psychologists should assist in the correct matching of intervention to the level of communication for the individual with RTT. The resource level of the intervention should be a stepped-up model of care.

Clinical Psychologists working with ID / RTT services should assist in supporting and upskilling other disciplines to firstly conduct practice based research and secondly utilise the most robust research methods and analysis available to increase research vigour of future studies. Finally Clinical Psychologists can promote and support disciplines to publish and disseminate their work.

Recommendations for future research

The review has highlighted the need for larger participant number research. This could be achieved by linking in with national and international RTT organisations and sourcing larger scale research funding. Future studies would benefit from increased research rigour including longitudinal data collection, multiple baselines, control studies and adequate follow up periods. Moreover, research should include information regarding the RTT stage, participant characteristics (such as age), demographics and report on how these might influence the research findings. Further, research regarding dose frequency of interventions should be conducted in order to achieve the optimum balance effective prompting methods versus the use of resources. Later, research developments should focus on expanding the communication skills of individuals with RTT to broaden their communication repertoires.

Future research into physiotherapy directed interventions is warranted to contribute to the knowledge base of physical fitness and mobility within RTT. In addition, further research is needed to investigate the efficacy of music therapy across larger sample sizes.

The early focus on parental involvement in interventions has diminished over the years, with increased focus on utilising recent advanced software. Given most children reside in the family home, a broader research focus is required to incorporate the impact of family and interaction interventions as opposed to solely software-led assistive technology. Future research should investigate interventions that have been researched within the remit of intellectual disabilities to investigate its utility in the RTT population. For example, there is a growing evidence base of the use of intensive interaction in individuals with severe and profound intellectual

disabilities. Research has reported on improved pre-verbal communication skills, maintenance of social engagement and relationships after an intensive interaction intervention (Anderson, 2006; Argyropoulou & Papoudi, 2012; Firth, Elford, Leeming, & Crabbe, 2008; Kellett, 2000, 2005; Samuel, Nind, Volans, & Scriven, 2008; Watson & Knight, 1991; Zeedyk, Caldwell, & Davies, 2009; Zeedyk, Davies, Parry, & Caldwell, 2009).

Conclusion

This review of a comparatively small number of studies that meet quality rating criteria, indicates that there is some evidence of effectiveness of interventions in RTT. The results need to be interpreted cautiously given the challenges of the research vigour. However the research presents promising insights into intervention programmes for individuals with RTT and future directions for clinical research.

Conflict of interest statement

The authors report no conflicts of interest

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References

Altman, D. G. (1991) *Practical statistics for medical research*. London: Chapman and Hall.

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

Anderson, C. (2006). Early communication strategies: Using video analysis to support teachers working with preverbal pupils. *British Journal of Special Education*, *33*(3), 114–120. http://doi.org/10.1111/j.1467-8578.2006.00426.x

Argyropoulou, Z., & Papoudi, D. (2012). The training of a child with autism in a Greek preschool inclusive class through intensive interaction: A case study. *European Journal of Special Needs Education*, *27*(1), 99–114. http://doi.org/10.1080/08856257.2011.640489

Auger, C., Hernando, V., & Galmiche, H. (2017). Use of Mechanical Insufflation-Exsufflation Devices for Airway Clearance in Subjects With Neuromuscular Disease. *Respiratory Care*, *62*(2), 236–245. http://doi.org/10.4187/respcare.04877

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

Cass, H., Reilly, S., Owen, L., Wisbeach, A., Weekes, L., Slonims, V., … Charman, T. (2003). Findings from a multidisciplinary clinical case series of females with Rett syndrome. *Developmental Medicine and Child Neurology*, *45*(5), 325–337. http://doi.org/10.1111/j.1469-8749.2003.tb00404.x

Centre for Reviews and Dissemination. (2009). Systematic reviews: CRD's guidance for undertaking systematic reviews in health care.

Cianfaglione, R., Hastings, R. P., Felce, D., Clarke, A., & Kerr, M. P. (2015). Psychological Well-Being of Mothers and Siblings in Families of Girls and Women with Rett Syndrome. *Journal of Autism and Developmental Disorders*, *45*(9), 2939–2946. http://doi.org/10.1007/s10803-015-2457-y

Einspieler, C., Freilinger, M., & Marschik, P. B. (2016). Behavioural biomarkers of typical Rett syndrome: moving towards early identification. *Wiener Medizinische Wochenschrift*, *166*(11–12), 333–337. http://doi.org/10.1007/s10354-016-0498-2

Firth, G., Elford, H., Leeming, C., & Crabbe, M. (2008). Intensive interaction as a novel approach in social care: Care staff's views on the practice change process. *Journal of Applied Research in Intellectual Disabilities*, *21*(1), 58–69. http://doi.org/10.1111/j.1468-3148.2007.00369.x

Fleiss, J., Levin, B., & Cho Paik, M. (2003). *Statistical Methods for Rates and Proportions*. *John Wiley & Sons*. http://doi.org/10.1198/tech.2004.s812

Guo, B., Moga, C., Harstall, C., & Schopflocher, D. (2016). A principal component analysis is conducted for a case series quality appraisal checklist. *Journal of Clinical Epidemiology*, *69*, 199–207.e2. http://doi.org/10.1016/j.jclinepi.2015.07.010

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

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

cases. *Annals of Neurology*, *14*(4), 471–479. http://doi.org/10.1002/ana.410140412

Hagberg, B., Witt-Engerström, I., Opitz, J. M., & Reynolds, J. F. (1986). Rett Syndrome: A suggested staging system for describing impairment profile with increasing age towards adolescence. *American Journal of Medical Genetics*, *25*(S1), 47–59. http://doi.org/10.1002/ajmg.1320250506

Kellett, M. (2000). Sam's story: Evaluating Intensive Interaction in terms of its effect on the social and communicative ability of a young child with severe learning difficulties. *Support for Learning*, *15*(4), 165–171. http://doi.org/10.1111/1467-9604.00170

Kellett, M. (2005). Catherine's legacy: Social communication development for individuals with profound learning difficulties and fragile life expectancies. *British Journal of Special Education*, *32*(3), 116–121. http://doi.org/10.1111/j.0952-3383.2005.00383.x

Lancioni, G. E., O'reilly, M. F., Singh, N. N., Sigafoos, J., Oliva, D., & Severini, L. (2008). Three persons with multiple disabilities accessing environmental stimuli and asking for social contact through microswitch and VOCA technology. *Journal of Intellectual Disability Research*, *52*(4), 327–336. http://doi.org/10.1111/j.1365-2788.2007.01024.x

Lancioni, G. E., O'Reilly, M. F., Singh, N. N., Sigafoos, J., Oliva, D., & Severini, L. (2008). Enabling two persons with multiple disabilities to access environmental stimuli and ask for social contact through microswitches and a VOCA. *Research in Developmental Disabilities*, *29*(1), 21–28. http://doi.org/10.1016/j.ridd.2006.10.001

Laurvick, C. L., de Klerk, N., Bower, C., Christodoulou, J., Ravine, D., Ellaway, C., … Leonard, H. (2006). Rett syndrome in Australia: a review of the epidemiology. *The Journal of Pediatrics*, *148*(3), 347–352. http://doi.org/10.1016/j.jpeds.2005.10.037

Leonard, H., & Bower, C. (1998). Is the girl with Rett syndrome normal at birth?

Developmental Medicine and Child Neurology, *40*(2), 115–121. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9489500

Mackay, J., Downs, J., Wong, K., Heyworth, J., Epstein, A., & Leonard, H. (2017). Autonomic breathing abnormalities in Rett syndrome: caregiver perspectives in an international database study. *Journal of Neurodevelopmental Disorders*, *9*(1), 15. http://doi.org/10.1186/s11689-017-9196-7

Marschik, P. B., Kaufmann, W. E., Sigafoos, J., Wolin, T., Zhang, D., Bartl-Pokorny, K. D., … Johnston, M. V. (2013). Changing the perspective on early development of Rett syndrome. *Research in Developmental Disabilities*, *34*(4), 1236–1239. http://doi.org/10.1016/j.ridd.2013.01.014

Matson, J. L. (2012). *Functional assessment for challenging behaviors*. New York: Springer.

Moga, C., Guo, B., & Harstall, C. (2012). Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique. Retrieved from http://www.ihe.ca/publications/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique

Moher D, A, L., & Tetzlaff J. (2009). Preferred Reporting Items for Systematic Reviews and Meta Analyses: The PRISMA Statement. *PLOS Medicine*. http://doi.org/10.1371/journal.pmed1000097

Neul, J. L., Kaufmann, W. E., Glaze, D. G., Christodoulou, J., Clarke, A. J., Bahi-Buisson, N., … Percy, A. K. (2010). Rett syndrome: Revised diagnostic criteria and nomenclature. *Annals of Neurology*, *68*(6), 944–950. http://doi.org/10.1002/ana.22124

Perelmutter, B., McGregor, K. K., & Gordon, K. R. (2017). Assistive technology interventions for adolescents and adults with learning disabilities: An evidence-based

systematic review and meta-analysis. *Computers & Education*, *114*, 139–163. http://doi.org/10.1016/j.compedu.2017.06.005

Reilly, S., & Cass, H. (2001). Growth and nutrition in Rett syndrome. *Disability and Rehabilitation*, *23*, 118–128.

Roland, L. T., Skillington, S. A., & Ogden, M. A. (2017). Sialendoscopy-assisted transfacial removal of parotid sialoliths: A systematic review and meta-analysis. *The Laryngoscope*, *127*(11), 2510–2516. http://doi.org/10.1002/lary.26610

Samuel, J., Nind, M., Volans, A., & Scriven, I. (2008). An evaluation of Intensive Interaction in community living settings for adults with profound intellectual disabilities. *Journal of Intellectual Disabilities*, *12*(2), 111–126. http://doi.org/10.1177/1744629508090983

Sigafoos, J., Green, V. A., Schlosser, R., O'eilly, M. F., Lancioni, G. E., Rispoli, M., & Lang, R. (2009). Communication intervention in Rett syndrome: A systematic review. *Research in Autism Spectrum Disorders*. http://doi.org/10.1016/j.rasd.2008.09.006

Sigafoos, J., Kagohara, D., Van Der Meer, L., Green, V. A., O'Reilly, M. F., Lancioni, G. E., … Zisimopoulos, D. (2011). Communication assessment for individuals with Rett syndrome: A systematic review. *Research in Autism Spectrum Disorders*, *5*(2), 692–700. http://doi.org/10.1016/j.rasd.2010.10.006

Simacek, J., Reichle, J., & McComas, J. J. (2016). Communication Intervention to Teach Requesting Through Aided AAC for Two Learners With Rett Syndrome. *Journal of Developmental and Physical Disabilities*, *28*(1), 59–81. http://doi.org/10.1007/s10882-015-9423-7

Watson, J., & Knight, C. (1991). An evaluation of intensive interactive teaching with pupils with very severe learning difficulties. *Child Language Teaching and Therapy*, *7*(3), 310–

325. http://doi.org/10.1177/026565909100700306

Witt Engerstrom, I. (1990). Rett syndrome in Sweden. Neurodevelopment-disability-pathophysiology. *Acta Paediatrica Scandinavica. Supplement*, *369*, 1–60. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1701067

Young, D., Nagarajan, L., de Klerk, N., Jacoby, P., Ellaway, C., & Leonard, H. (2007). Sleep problems in Rett syndrome. *Brain and Development*, *29*(10), 609–616. http://doi.org/10.1016/j.braindev.2007.04.001

Zeedyk, M. S., Caldwell, P., & Davies, C. E. (2009). How rapidly does Intensive Interaction promote social engagement for adults with profound learning disabilities? *European Journal of Special Needs Education*, *24*(2), 119–137. http://doi.org/10.1080/08856250902793545

Zeedyk, M. S., Davies, C., Parry, S., & Caldwell, P. (2009). Fostering social engagement in Romanian children with communicative impairments: The experiences of newly trained practitioners of Intensive Interaction. *British Journal of Learning Disabilities*, *37*(3), 186–196. http://doi.org/10.1111/j.1468-3156.2009.00545.x

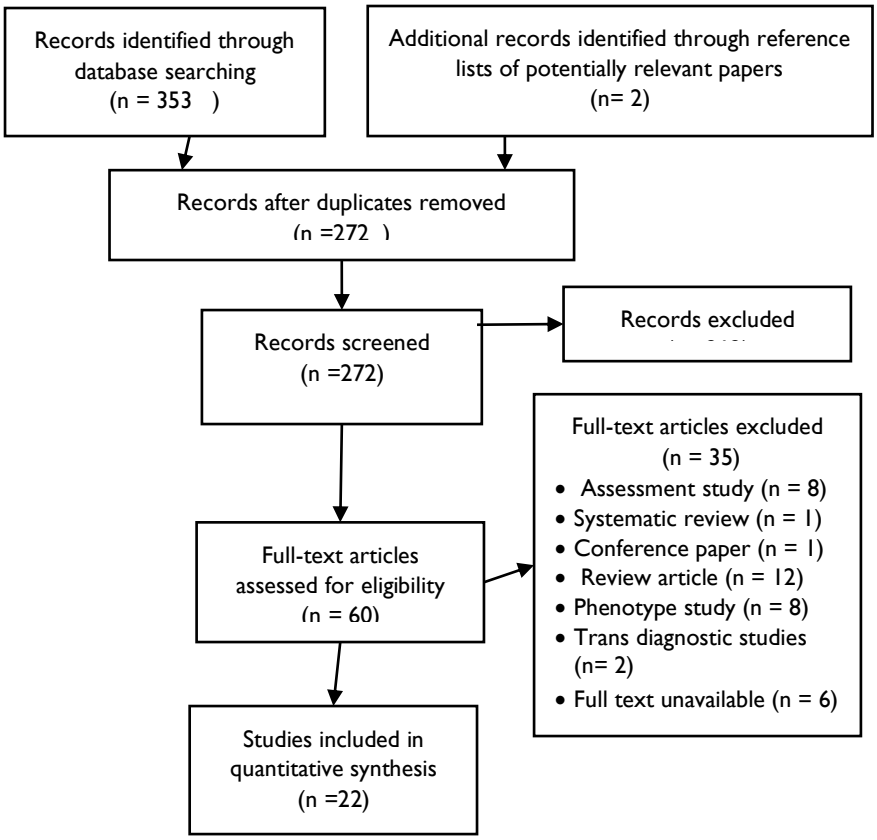

Figure 1. PRISMA flow diagram

Table 1. Sample characteristics data table

No	Study	Cohort Characteristics	Current Functioning	Setting
1	(Sharpe & Ottenbacher, 1990)	N=1, F, Aged 5	No significant speech, unsteady gait, severely delayed fine motor skills, feeding assistance	School
2	(Sharpe, 1992)	N=2, F, Aged 5	N1 stereotypic hand-to-mouth and rocking behaviours. N2 stereotypic hand-to hand behaviour patterns, would attempt to grasp a cracker when placed in front of her using a rhythmical raking-mass grasp pattern while maintaining a modified version of the stereotypic hand behaviour. Neither subject demonstrated any functional hand movements. Neither subject had ever used hand splints.	School
3	(Margaret Wolan Sullivan, Laverick, & Lewis, 1995)	N=1, F, Aged 3	Unable to walk or talk. Some eye contact and some social smiling.	School
4	(Evans & Meyer, 1999)	N=1, F, Aged 5	Described as 'severely mentally retarded' with limited social and communication (no expressive verbal language or formal communication skills. Ambulatory and unable to grasp objects. Repetitive hand mannerisms.	Special education programme
5	(Koppenhaver et al., 2001)	N=6, F's, Aged 3-7	All exhibited severe communication impairment as evidenced by limited to no intelligible speech. N=1 Spoke, looked at people or objects to indicate attention, wants, or needs. N=2-6 Communicated through a variety of nonconventional gestures and vocalizations. N 1-3 Were able to ambulate independently, N- 4-5 required physical assistance such as hand-holding and N6 used a manual wheelchair that she could not self-propel. A participants were perceived as functioning in the range of severe to profound mental retardation.	School
6	(Yasuhara & Sugiyama, 2001)	N=3, F, Aged 4-6	All no speech ability and able to sit by self.	Hospital
7	(Hetzroni, Rubin, & Konkol, 2002)	N=3, F, Aged 8-10	All Stage III, non-verbal and used various communication methods. N1 no functional use of her hands and no functional speech, walks with a wide gait, explores the classroom independently and interact with adults by approaching them. N2 walk with a wide gait, but tended to walk asymmetrically. No functional use of hands and no functional speech. Appeared to make choices by gazing at graphic representations of objects. N3 walked independently, with unstable gait and some assistance. Some vocalisation, but no functional use of her hands. Able to point head to indicate choice	School
8	(Elefant & Lotan, 2004)	N=1, F, Aged 9	Walks with considerable support and sits with external support. No alternative communication system or even minimal communicational abilities. Gazes unfocused in space and smiles. Some vocalization, which increase when she is being sung to, when she is excited, and when her vocalization is being imitated.	Not stated
9	(M Lotan, Isakov, & Merrick, 2004)	N=4, F, Aged 8-11	Rett Stage III (no further information provided)	School
10	(Elefant & Wigram, 2005)	N= 7, F, Aged 4-10	Six girls were in stage III, the 'plateau stage' of whom two are not ambulant. One girl was in stage IV, the 'late motor deterioration stage'.	Not stated
11	(Bergström-Isacsson, 2007)	N=21, 20F, 1M, Aged 3-44	None mentioned	National Rett Centre
12	(Fabio, Giannatiempo, Oliva, & Murdaca, 2011)	N=12, F Aged 6-26,	All in post-regression phase, severely mentally retarded, and unable to speak. All showed little or no purposeful hand use and had pervasive hand stereotypies. Ambulation was preserved in all girls.	School

13	(Meir Lotan, Schenker, Wine, & Downs, 2012)	N=3, F, Aged 3-5	None reported	Not stated
14	(Bartolotta & Remshifski, 2012)	N=4, F, Aged 5-14	Clinical Stage III (pseudostationary period). Three participants were reported to vocalize (no word production) and able to use augmentative and alternative communication (AAC) strategies (opportunities for choice making, use of single switches and picture boards). All girls were reported to use eye gazing for communication purposes.	School
15	(Fabio, Castelli, Marchetti, & Antonietti, 2013)	N=1, F, Aged 21	Clinical stage IV of RS. Can walk / run for hours turning in a room, no meaningful words or eye contact. Inability to hold, pick up or grasp objects, hand stereotypes.	School and home
16	(Stasolla & Caffò, 2013)	N= 2, F, Aged 12-17	Both participants lack of speech, hyperventilation, withdrawal, stereotyped behaviours (i.e., body rocking for N1 and hand washing for N2), scoliosis, seizures, epilepsy. Motor impairments with dystonic movements, although they were able of some step responses in their walker device. Severe to profound intellectual and developmental disabilities. Some vocalizations, limited use of hands, profound deficits in adaptive behaviours	Home
17	(Hackett, Morison, & Pullen, 2013)	N=1, F, Aged 4	No purposeful hand movements, no eye contact	Not stated
18	(Stasolla et al., 2014)	N=3, F, Aged 8-10	Communication impairments (i.e. lack of speech, but some vocalizations), seizures, hyperventilation, withdrawal, stereotyped behaviors (i.e. body rocking for n1, hand tipping for n2 and hand washing for n3). None of the girls had awareness of the sphincteric control and all motor impairments, with failure in ambulation responses. Severe to profound developmental disabilities. Unable to perform request and choice of needed items to communication partners.	Home
19	(Lancioni et al., 2014)	N=1, F, Aged 21	No speech or communication. No interaction with objects. Non ambulatory. Sat in wheelchair.	Home
20	(Stasolla et al., 2015)	N=3, F, Aged 9-12	Lack of speech, autonomous locomotion. Severe to profound developmental and intellectual disabilities. Repetitive hand stereotypic behaviours but able to pick up familiar objects.	Home
21	(Simacek, Reichle, & McComas, 2016)	N= 2, F, Aged 7-27	Unable to use gestures or vocalisations, able to display idiosyncratic responses that allowed researchers to assess preference for items and / or activities	Home
22	(Simacek, Dimian, & McComas, 2017)	N=1, 3 year old girl*	Ambulatory, with gross motor abilities to walk, step up and down to navigate stairs with supervision, and to bend down and pick up or briefly hold small items. Hand function ability included self-feed and pick up light-weight items and to press buttons to activate musical toys. Frequent repetitive behaviours of clasping hands, mouthing hands, and mouthing other objects.	Home

*Two further participants with Autism Spectrum Disorder

Table 2. Study characteristics data table

No	Article	Target Behaviour and variables	Design	Measures	Intervention	Results	Quality Score (0-15)
1	(Sharpe & Ottenbacher, 1990)	*Physical / Movement* IV-Elbow restraint DV-Feeding ability	Single Study ABAB	Finger feeding skills	Elbow Restraint	Modest improvements in amount of cereal consumed and in time required to complete task	8.5
2	(Sharpe, 1992)	*Physical / Movement* IV-Hand splints and elbow othosis DV-stereotypic movements and toy use	Mutiple-baseline	Observation of stereotypic behaviour and hand wringing	Hand Splint	1) No decreased stereotypic movements 2) No increased feeding skills 3) No increase in handwringing following withdrawal	7.5
3	(Margaret Wolan Sullivan et al., 1995)	*Communication* IV-Contingency intervention programme DV-positive emotional response	None stated	Head and hand activation frequency	Contingency intervention programme (Margaret W. Sullivan & Lewis, 1993)	Modest and inconsistent increase in hand use	5.5
4	(Evans & Meyer, 1999)	*Behaviours* IV – Individualised Intervention programme DV –Hand stereotypes (1) and development of informal gestures (2)	ABAB	1)Frequency of behaviours; body rocking, hand mannerisms, rubbing face, mouthing body, cry, shriek, blowing & vocalising 2)Frequency of gestures	Individual educational plan (IEP) including non-contingent restraint of hand mannerisms and use of standard prompting and social reinforcement	1)No reduction in behaviours and restraint increased use of other behaviours (blowing) 2) No evidence of hand gesture acquisition Procedure, intervention and results only discussed in narrative form, resulting in challenges in interpretation and standardisation of the methodology.	8.5
5	(Koppenhaver et al., 2001)	*Communication* IV-Story book intervention DV-Communication ability	Multiple-baseline	Coding of storybook interactions coded by communication mode and communication act (e.g.use of picture symbols and speech-generating devices to label pictures)	Introduction of a variety of assistive technologies on the storybook reading and communicative interactions. Parental training of story book interactions (including attribute meaning to communicative attempts, ask questions to encourage communication and use of time delay and prompts to	Substantial increases in frequency of symbolic communication and labelling commenting were reported in all six participants without highly structured or long-term interventions. Symbolic communication, increased with frequency of (1) introduction of communication technologies; and (2) increasing mothers' awareness of communication modes of their daughters. However there was no sessional data available and the intervention was not strictly controlled for.	**9***

					encourage accurate use of speech generating device.		
6	(Yasuhara & Sugiyama, 2001)	*Communication* IV-Music therapy DV-Hand grasping	No evidence of experimental design	Coding of recorded sessions	Individualised music therapy including instrument play, engagement in song and choices.	The authors report that the music therapy showed a degree of mental and physical development. However there was no evidence of operationally defined behaviours or treatment.	5
7	(Hetzroni et al., 2002)	*Communication* IV-Assistive technology DV-learning	Multiple probe design	Symbol set identification	Use of individualised computer-based augmentative and alternative communication (ACC) system (choice of picture symbol or word by using eye gaze and moving nose or head.	The authors report a steady learning curve across symbol sets and a partial retention of knowledge throughout maintenance probes. The results suggest that girls with Rett syndrome are capable of matching spoken words to symbols when provided with meaningful instruction. However some baseline results also improved, therefore improvements should be interpreted cautiously.	**10***
8	(Elefant & Lotan, 2004)	*Communication* IV-Music and physical therapy DV-Attention span and communication (non-verbal expression, vocalization and verbal ability)	None stated	None clearly defined	13 phase combined music and physical therapy	The authors state the intervention approach has proved effective in improving communication skills. However the study was reported in narrative form and did not include an experimental design, outcome measures or include data.	3.5
9	(M Lotan et al., 2004)	*Physical / Motor* IV- Physical Exercise Programme DV-Physical fitness and general functioning	Paired t-test pre and post design	Pulse measurements and functional skills scale.	Treadmill training	Improved physical fitness and general functional abilities. High correlational linkage between functional improvement and physical fitness.	**10.5***
10	(Elefant & Wigram, 2005)	*Communication* IV-Music therapy DV-Learning and communication ability	A single subject, multiple probe design	Observed frequency of communication of selection (eye gaze, nose pointing, touching picture / words)	Music therapy including song selection (from symbols) and confirmation of selection	The authors report evidence of learning in all participants and responses to music therapy. However, this research did not present baseline data and provide the data to support their conclusions (apart for one participant).	7.5
11	(Bergström-Isacsson, 2007)	*Communication* IV – Music and vibroacoustic therapy(VT) DV- Brainstem activity	Controlled within-subject study	Brainstem Activity (Parasympathetic and sympathetic responses)	Music therapy and VT	Overall, "calming music" evoked parasympathetic responses and "activating music" evoked sympathetic responses in the responders. Horn music and vibroacoustic were effective stimuli that evoked responses in all the subjects in this group. Calming music	**10***

						together with the vibroacoustic stimulus for dual stimulation, became less effective and failed to evoke autonomic responses in some subjects.	
12	(Fabio et al., 2011)	*Communication* IV-Attention training DV-Requests and attention	Pre-test, post-test study design.	Attention span coding, frequency of help given, Vineland score and the number of correct answers	Attentional training	Reported it is possible to modify attention span and decrease the dependence on help in cognitive training. Controlling posture and physical containment decreases stereotypies (necessity to remove all external stimuli that make it difficult to work on the target stimulus, thus, enhancing their selective attention). Increase on most of the Vineland areas (communication, daily ability, socialization and motor skill).	**10***
13	(Meir Lotan et al., 2012)	*Physical / Motor* IV – Motor skills intervention DV- Physical improvements	AB design	The Rett Functional Evaluation Scale and Rett Syndrome Gross Motor Scale. Functional performance in the domains of self-care and social function were assessed using the Paediatric Evaluation of Disability Inventory (PEDI), Hand function was measured with a scale developed based on the Hand Apraxia Scale.	Conductive Education (CE). An educational approach aimed to improve psycho-social development, co-ordination, motor control and activity participation. The specific nature of the intervention was not described.	The authors report improvements in gross motor function, whilst there does seem to be modest improvements, the improvements were not tested statistically. Hand function and social skills were similar at baseline and 16/17 months following intervention. Self-care skills were the same or declined (n1) following the intervention period.	8.5
14	(Bartolotta & Remshifski, 2012)	*Communication* IV – Coaching communication partners to recognise and respond to communication acts DV – Communication behaviours	Quasi-experimental repeated measures design	Frequency of communication behaviours (vocalisations, head and body movements, gestures, facial expressions, or use of AAC strategies)	Coaching sessions over four phases (baseline, coaching intervention, post coaching session and follow up maintenance) using recorded data and data analysis of behaviours and AAC strategies.	The increase in the communication partners' awareness (following coaching) of the girl's communication attempts corresponds with a change in the communication partners' behaviour and a change in the child with RTT's communicative behaviour.	8
15	(Fabio et al., 2013)	*Communication* IV-Cognitive rehabilitation training DV-Read writing ability	Single case research. Short time series design	Number of attempts to reach criteria for words, letters and syllables	Cognitive rehabilitation training based on Feuerstein's modifiability and mediated learning theory (Feuerstein, Rand, & Rynders, 1988). Intervention was run over two	Learning of 16 specific words (names and familiar objects) and reading syllables.	**10***

					phases pre-training and training.		
16	(Stasolla & Caffò, 2013)	*Communication* IV-Assisted technology DV-Performance, happiness and reduction in stereotypes	Multiple probe design	Frequency of microswitch activation, indices of happiness and indices of stereotyped behaviours	Assisted technology (microswitch) for five minutes 3-4 times per day over six months.	Increase of performance of microswitch use and of indices of happiness and a decrease of stereotyped behaviors for both participants during intervention phases.	**11***
17	(Hackett et al., 2013)	*Communication* IV- Music therapy DV – Hand use and turn taking	Single case retrospective video analysis	Frequency of hand use and turn taking	Music Therapy over 14 sessions.	Increased frequency of hand use and turn taking.	**9***
18	(Stasolla et al., 2014)	*Communication* IV – PECS and VOCA DV - Communication	Alternating treatment single case design	Number of items requested and chosen independently, Stereotyped behaviours, and Indices of happiness.	PECS sessions and VOCA sessions	PECS and VOCA improve communication abilities via the introduction of making request and choice of items. Both intervention strategies are successful by increasing participants' positive mood (i.e. indices of happiness) and by reducing stereotyped behaviours.	**11***
19	(Lancioni et al., 2014)	*Communication* IV – Assisted technology {microswitch) DV- Microswitch responses and level of happiness	ABAB	Level of response and stimulation input and objective measures of happiness	Microswitch assisted technology	Increase in microswitch responses and level of happiness for both participants during the intervention phases of the study.	**10***
20	(Stasolla et al., 2015)	*Communication* IV – Assistive technology DV- Responses and stereotypes behaviour	Multiple probe design	1. Number of objects inserted in a container 2. Happiness indices 3. Intervals of stereotypic behaviours	Assisted technology (sensors and personal computer)	Reduction in stereotypic behaviours, increase in adaptive responses and increase in indices of mood.	**9***
21	(Simacek et al., 2016)	*Communication* IV-AAC intervention (Speech generated device with eye gaze or touch screen technology) sessions DV - Responses	Case series. Within participant using concurrent multiple baseline design	Independent accurate selection (via pressing or eye gaze) of target request	Use of speech generated device (SGD) to increase aided AAC using either pressing (n1) or eye gaze (n2) to select preferred item or choice	Acquisition of requesting skills for n=1 which were sustained. Increasing of skills in n=2, however the skills were not sustained when prompt was faded.	**11***
22	(Simacek et al., 2017)	*Communication* IV-Parent-implemented communication intervention with	Adapted multiple-probe design with an	AAC responses (hitting a microswitch) and individual idiosyncratic responses (Hitting the tray of high chair, extending one or both hands towards	Parent-implemented Functional Communication Training (FCT) with Telehealth as a	AAC response was learnt across three contexts. However the participant with RTT did not retain the learning of responses. The authors propose that different reinforcement schedules might further assist	**9***

		remote coaching via telehealth DV-Augmentative and alternative communication (AAC) responses	embedded ABAB design	parent or item and walking towards parent)	service delivery mechanism	learning following intervention. In addition the need for future research of intervention fading strategies.	

**Rated acceptable quality and included in the review*

Paper 2

The prevalence of attenuated behaviours in Rett Syndrome and Rett Episodes

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Prepared in accordance with author guidelines of the Journal of Intellectual Disability Research (Appendix 2). This journal follows Harvard reference style.

Word Count: 5114

Abstract

Background: Recent research into attenuated behaviours [Autistic Catatonia] has identified its prevalence in people with genetic neurodevelopmental condition including Cornelia de Lange Syndrome (CdLS) and Fragile X syndrome (FXS). The current study investigated the prevalence of attenuated behaviour with Rett Syndrome (RTT) and in particular, its presence during what are termed 'Rett Episodes'.

Method: The Attenuated Behaviour Questionnaire (ABQ) was fully completed by parents of 28 individuals with RTT. The ABQ was completed twice, to indicate the prevalence of attenuated behaviours during 'typical behaviour' and during 'Rett Episodes'.

Conclusions: The findings reveal that attenuated behaviour is present within the RTT population across all core symptoms. The presence of attenuated behaviour is not associated with 'Rett Episodes'. Clinical implications and future research are discussed.

The study further investigated the prevalence of attenuated behaviours in RTT compared to other neurodevelopmental conditions. Attenuated behaviours as rated by the ABQ were found to be higher in RTT than in other neurodevelopmental conditions (ASD, CdLS and FXS). The results indicate that the severity of attenuated behaviours is negatively correlated with age.

Key words: Rett Syndrome, genetic syndromes, attenuated behaviour, Rett Episodes, movement disorder, catatonia.

Background

Rett Syndrome (RTT) is a rare genetic disorder that occurs almost exclusively in females with an incidence of one in every 10,000 live female births. It is characterised by severe cognitive and physical impairments. It is diagnosed clinically and is usually associated with a mutation in the methyl-CpG binding protein-2 (*MECP2*) gene (Amir et al. 1999). Classic RTT is characterised by apparently normal psychomotor development over the first six months followed by four developmental stages (Hagberg 2002; Hagberg et al. 1983; Hagberg et al. 1986; Neul et al. 2010; Witt 1990). Stage I is a stagnation of psychomotor development (early onset stagnation) typically occurring between six and eighteen months. This is followed by a regression of acquired skills or communication between the age of 1 to 3 or 4 years (stage II developmental regression) which develops over weeks or months. The phase of regression is inherent to RTT - by definition - and comprises the partial or complete loss of previously acquired purposeful hand skills, gait irregularities and the development of stereotypic hand movements such as hand wringing, clapping and tapping (Neul et al. 2010). The regression also involves a period of social withdrawal or impaired communication. This is followed by a period of stabilization (stage III pseudo stationary period) or some degree of recovery. Stage IV can follow years or decades after stage III and results in motor deterioration. Within the RTT population, there are vast variations of clinical severity (Foley et al. 2011). This variation has been linked to specific genotypes (Bebbington et al. 2008; Neul et al. 2008).

Other clinical features of RTT include autonomic abnormalities such as breath holding, hyperventilation and abdominal bloating (Mackay et al. 2017), impaired sleep, growth retardation and periods of inappropriate laughing / screaming (Cass et al. 2003; Cianfaglione et al. 2015; Neul et al. 2010; Reilly & Cass 2001; Young et al. 2007). In addition, individuals

with RTT are reported to experience epileptic seizures with cumulative prevalence rates ranging from 50-94% (Cooper et al. 1998; Hagne et al. 1989; Jian et al. 2007; Steffenburg et al. 2001; Witt 1992), although the point prevalence is certainly much less (Tarquinio et al 2017). Unusual electroencephalographic (EEG) activity patterns for girls with RTT typically develop and change as the condition progresses. At Stage I of the condition (approximate age range 6-18 months) normal EEG activity is usually found. At stage II some abnormal focal spikes are found often followed by some epileptic behavior, however by stage III and IV individuals are found to have considerable abnormal EEG activity (Hagne et al. 1989).

Alongside the presence of epilepsy, non-epileptic vacant episodes have consistently been reported (Cardoza et al. 2011; Cooper et al. 1998; Glaze et al. 1998; Hagberg et al. 1983; Hagne et al. 1989; Witt 1992). Such Rett Episodes [RE] (Cardoza et al. 2011; Glaze et al. 1998) involve non-epileptic behaviours such as distant eye gaze, apparent absences (e.g. appearing 'vacant'), twitching, jerking or dystonic posturing of the hands, arms, head or other parts of the body and apparent breath holding (Cardoza et al. 2011; Glaze et al. 1998) and appear to be present in about 74% of cases of RS (Cardoza et al. 2011). Glaze et al. (1998) found that often RE were misrepresented as epileptic seizures when clinical observations were compared to EEG activity. The etiology of RE is not yet understood and putative explanations include abnormal motor activity, or manifestations of autonomic nervous system dysfunction (Glaze et al. 1998) and it is noted that atypical brainstem functioning such as eye movements, facial twitching and vacant spells are present during RE (Julu et al. 2008).

Research into the clinical cross overs of different genetic syndromes have been important in assisting research and practice into syndrome-related phenotypes. For example, research into non-epileptic paroxysmal events in RTT (Cardoza et al. 2011; Glaze et al. 1998) and Autism

Spectrum Disorder (ASD) (Kim et al. 2006; Parmeggiani et al. 2010) have assisted in the recognition and future proposals for the identification of non-epileptic paroxysmal events in Pallister-Killian Syndrome (Filloux et al. 2012). In the case of ASD, research into 'autistic catatonia' (Billstedt et al. 2005; Breen & Hare 2017; Ghaziuddin, Quinlan 2005; Realmuto & August 1991; Wing & Shah 2000) has found that between 6-8% of adults with ASD display catatonic-like behaviours (Wing & Shah 2000) including increased slowness affecting movement and verbal responses, difficulty in initiating and completing actions, increased reliance on physical or verbal prompting by others and increased passivity and apparent lack of motivation. These catatonic-like or attenuated behaviours may be part of the wider ASD behavioural phenotype rather than a separate co-morbid condition (Hare & Malone 2004; Realmuto & August 1991) and have been operationalised via the development of the *Attenuated Behaviour Questionnaire* (Breen & Hare 2017) which has facilitated research in other developmental disorders that are highly associated with ASD. Bell et al (2018) examined attenuated behaviour in Cornelia de Lange syndrome (30% prevalence) and Fragile X syndrome (11% prevalence) and found the presence of repetitive behaviours to be a predictor of risk factors for attenuated behaviours in both cases. The current study aims to extend this research by examining the prevalence of attenuated behaviours in RTT and the relationship with Rett episodes. This will be the first study investigating attenuated behaviours in RTT.

Research Aims and Hypotheses

The primary aims of the present study were to (1) determine the prevalence of attenuated behaviour in RTT using the Attenuated Behaviours Questionnaire (ABQ) (Breen & Hare 2017), (2) to investigate any difference between attenuated behaviour when the individual is experiencing a RE and when they are not experiencing a RE (hereafter referred to as non-RE), (3) identify which of the core features of attenuated behaviour were most typical within

RTT, (4) determine if there is an association between AB severity and age and (5) compare the prevalence rates of AB in RTT and other genetic conditions. Based on behavioural phenotypes into RTT, it was hypothesised that attenuated behaviour would be present in RTT (hypothesis 1) and attenuated behaviours would be more present during RE (hypothesis 2). In the absence of research into the core features of attenuated behaviours in RTT no *a priori* hypotheses was made regarding the third aim. Given the regression in functioning in RTT it was hypothesised that there would be an association between severity and age (hypothesis 3). No a priori hypotheses were made regarding the prevalence of attenuated behaviours in comparison to other genetic conditions.

Methods

Measures

Attenuated Behaviour Questionnaire (ABQ) (Breen & Hare 2017)

This is a 28-item third party report measure developed by Breen & Hare (2017). The ABQ aims to identify the presence of attenuated behaviour (i.e. behaviours akin to autistic catatonia) in individuals with genetic conditions. The core domains have been found to show discriminatory validity and concur with earlier diagnostic criteria for autistic catatonia (Wing & Shah (2000). The items in the ABQ assess motor symptoms, affective alterations and behavioural alterations. All items are supported by behavioural descriptions and rated on a Likert scale ranging from 0-4 (*0=-No, never observed; 1= No, not at the moment but it used to happen; 2=Yes but less than before; 3=Yes, the same as before; 4= Yes, more than before*). The first six items are the most commonly reported motor movement dysfunction symptoms and are considered the 'core items'. The ABQ identified attenuated behaviour on the basis of three or more core items of attenuated behaviours being present as rated 2, 3, or 4 (Breen

& Hare 2017). A presence of the 'core item's' allows for further information to be collated, about the frequency and severity of the symptom via additional questions. The frequency rating asks *how often does the individual experience periods of [symptom] at the moment?* Which is rated from the following options:

- All or almost all of the time they are awake
- Most of the time they are aware
- Some of the time they are awake
- Rarely when they are awake

The severity rating enquires *how severely does the individual experience these periods of [symptom] at the moment?)*. The range will be rated from the following;

- Very severely – they seem unable to focus on or do anything else at these times
- Quite severely – it is difficult for them to focus on anything else at these times
- Moderately- there seems to be an effect on their ability to focus on or do things
- Slightly – this seems to have little or no effect on their life

The current study investigated the six core attenuated behaviour domains for their presence, frequency and severity.

Breen & Hare (2017) have found the ABQ to hold 0.65 sensitivity and 0.38 specificity for existing diagnoses of autistic catatonia.

Rett Episode Questionnaire (REQ)

Although there is no formal diagnostic criteria, RE have been described on the basis of clinical observations (Cardoza et al. 2011; Glaze et al. 1998) and the REQ was compiled for the purposes of the present study. The REQ questionnaire asks participants to identify if their child had experienced a RE, and if so, about the nature of the episodes. For example, do they look like seizures, episodes with disturbed breathing, or other episodes with altered awareness, color change, agitation, calmness or distress. Participants were further asked how many different types of episodes they have and they were asked to clarify the duration, frequency and mode of onset.

Demographic Questionnaire

The demographic questionnaire gathered information relating to parents / carers age, sex, ethnicity and relationship to the individual with RTT together with information relating to their child's age, sex, ethnicity and current living environment.

Participants

Parents or carers of individuals diagnosed with RTT were recruited via an existing research database (the British Isles Rett Syndrome Survey) held by The Institute of Medical Genetics, Cardiff University. Parents or carers of individuals on the database had consented to be approached about future research projects. Parents (N=290) who had been contacted for a recent research study (Cianfaglione et al. 2015) were contacted via post and invited to participate in the research. There were no exclusion criteria for the study. A total of 290 parents and carers were posted a covering letter, a research pack and a stamped addressed envelope to return the completed questionnaire. The research pack included a participant information sheet, consent form, demographic questionnaire, two copies of the ABQ, and the

REQ. Further recruitment was undertaken using online social media via Rett UK and The Rett Association of Ireland. Three social media support groups for parents and carers of individuals with RTT were also approached to participate in the research. The online links included the identical information that was sent in the research pack.

Procedure

The participants needed to complete two ABQ's, one with ABQ with RE in mind and one with typical everyday behaviour (named non-RE) in mind. To control for order effects of the completion order the postal and online questionnaires were randomly assigned. Those individuals who did not declare that their child experienced RE were asked to complete the ABQ with non-RE in mind only.

Ethical approval

The study was approved by the Research Ethics Committee, School of Psychology, Cardiff University.

Data analysis

All data were anonymised and analysed in compliance with the Data Protection Act (1998). Data were analysed with *Statistical Packages for the Social Sciences* version 23. Incomplete datasets were recorded for five participants, who were omitted from the subsequent analyses.

A priori power analysis using 0.05 p value was completed via G*Power software (Faul. et al. 2007) prior to the study completion. A large effect size was chosen to be consistent with

previous studies using the ABQ namely Bell et al (2019) and Breen and Hare (2017) who reported a moderate to large effect size. The analysis indicated that a sample size of 23 (for parametric paired t-test) and 24 (for non-parametric Wilcoxon Signed Rank Test) would be required for a large effect size (0.8). The sample sizes exceeded this and as such the study was powered (Cohen, 1988).

The Shapiro-wilk test was used to test for normality of data on continuous variables. When parametric assumptions were met a paired t-test was used. If they were not met The Wilcox signed rank test was conducted on continuous variables that were non parametric (frequency of core symptoms). Whereas a paired t-test with bootstrapping based on 2,000 samples was conducted on parametric continuous variables (severity scores). Dichotomous variables were tested using a McNemars Test (presence of AB above cut off). A Pearsons Correlation Coefficient was used when data met parametric assumptions to examine the relationship between variables (attenuated behaviour and age).

Results

Demographic data

A total of 290 potential participants from the research database were contacted of whom N= 24 (8.3%) took part in the current study. A total of 32 (11%) envelopes were returned to sender, commending that the addresses no longer lived at the address and they did not have a forwarding address. One family contacted the research study expressing their child had since passed away. An additional nine participants were recruited using online measures, providing a total of N=33 participants in the study.

Continuous variables were checked for normal distribution using the Shapiro-Wilk Test. The age of participants (carers) was found to deviate from normality ($D(31) = .157$, $p<0.05$), whilst the age of those affected by Rett syndrome (their children) was found to be normally distributed ($D(31)= .152$, $p>0.05$).

As expected, all of the children with RTT were female. In total, N= 32 of the parents (97%) were female and white British. The majority of individuals with RTT lived with their family (N=26, 78%) with seven (21%) living with other carers. It was presumed that, as all respondents were co-resident with their child, they would be able to report accurately on their child's symptoms and behaviour.

Rett Episode Data

29 of the parents (88%) reported that their child had experienced a RE with three reporting no RE and one unsure.

Rett Episode Validation

The qualitative descriptions of RE were collated and analysed by a clinical geneticist (AC) with extensive experience in the field of RTT. Participants described RE both of a single and multiple type and often experience epileptic seizures as well as RE. Disturbances of breathing rhythm and environmental triggers of the RE were commonly reported. RE were speculated to be triggered by anxiety-provoking circumstances, and the accompanying breath-holding.

Examination of presence of attenuated behaviour during RE and non-RE

The ABQ had missing data (5/33) for the questions of which they were not valid for their child (e.g. child was immobile). The ABQ 'everyday behaviour' was completed for 28 participants and the ABQ for RE was completed by 26 participants. Breen & Hare's criteria (2017) were used to examine core features of attenuated behaviour. On this basis, attenuated behaviour was present during non-RE in N=17 (65%) across all core symptoms (mean=3.18, sd=1.74) whilst attenuated behaviour during RE was present in N=20 (77%) again across all core symptoms (mean=3.54, sd1.94).

The severity (weighted scores) of the core scores during non-RE (mean=9.61, sd=5.64) and during RE (mean=10.88, sd=6.69).

A Shapiro-Wilk test indicated the data were normally distributed for the severity scores in both non-RE (D (26) = 0.972, p>0.05) and during RE (D (26) = 0.583, p>0.05). The data was found to be normally distributed in the non-RE score (D (26) =944, p>0.05) but not for the frequency score of RE (D (26) = 0.912, p<0.05).

There was no statistically significant difference between the frequency of core symptoms for non-RE and during RE (z=1.260, p=0.208). A paired t-test with bootstrapping revealed there was no significant difference between the severity of the core scores between the two time frames (t=1.356, df=25, p>0.05). The difference in prevalence within the group during RE and non-RE was found to be not significant (p=0.25). Therefore there does not appear to be any difference in presence of attenuated behaviour during RE.

Core attenuated behaviour symptom presentation

Figure 1 presents the frequency of each core symptom within the sample. The histogram shows that all of the core symptoms of attenuated behaviour were present across the whole sample. The most highly reported was physical and/or verbal prompts needed (n=23, 82%). The other symptoms were reported as present in 46-57% (n=13 to n=16) of the sample.

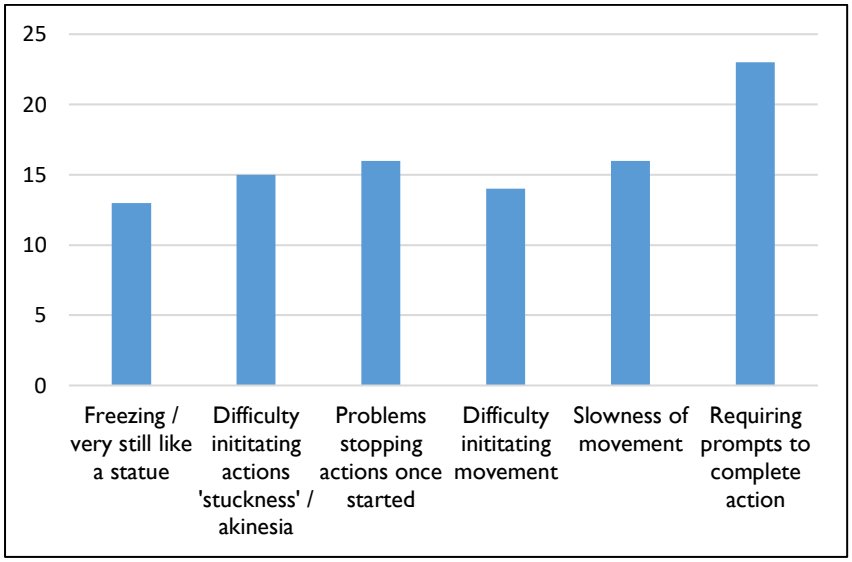

Figure 1: Histogram of core attenuated behaviour symptom presentation (n=28)

Attenuated behaviour and age

Age was found to be significantly correlated with ABQ frequency (r=-.372, n=28, p.0.05) and ABQ severity (r=-.425, n=28, p<0.05) score (Figs. 2 & 3). This indicates a medium effect size (Cohen. 1988)

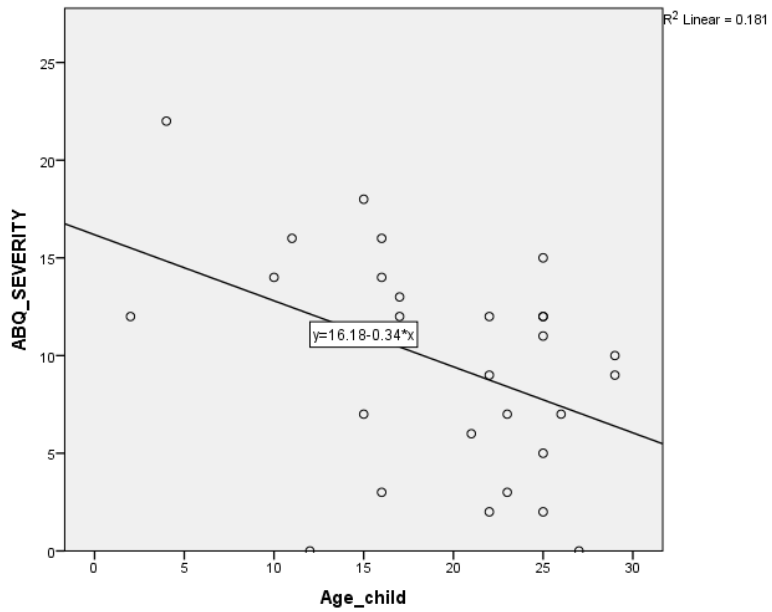

Figure 2: Scatterplot exploring the relationship between ABQ severity scores and age

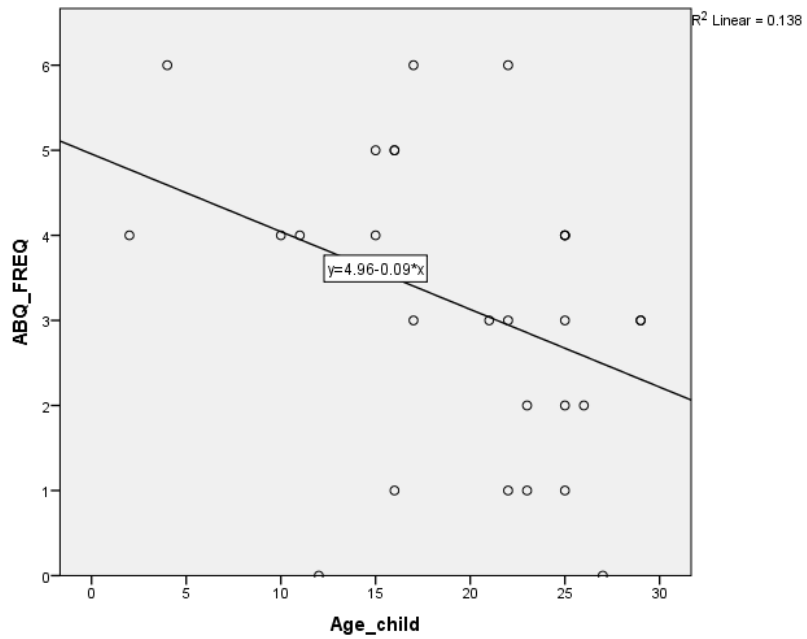

Figure 3: Scatterplot exploring the relationship of the ABQ frequency scores and age

Attenuated behaviour prevalence rates in different genetic conditions

Prevalence rate of attenuated behaviour in RTT in the current study, as measured by the ABQ (i.e presence of three of more core symptoms), was compared with pre-existing research

reporting ABQ data for ASD, CDLS and FXS (Bell et al. 2018) (Figure 4). RTT had the highest prevalence rate (17/28) followed by ASD (48/49), CDLS (10/33) and FXS (8/69).

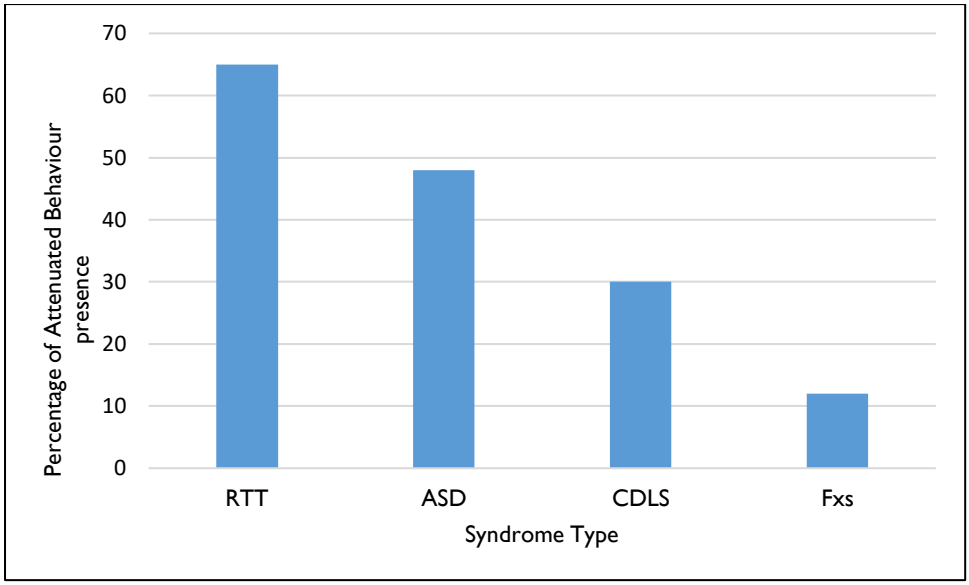

Figure 4: Chart of prevalence rates of Attenuated Behaviour prevalence rates across conditions

Discussion

The current study had five objectives, namely to examine the prevalence of attenuated behaviour in RTT, to investigate the incidence of attenuated behaviour across RE and non-RE, to identify which core attenuated behaviour features were most prevalent, to examine the relationship between attenuated behaviour severity and age and finally to examine the presence of attenuated behaviour across previous research in other genetic conditions. With regard to aim and hypothesis 1, attenuated behaviour was present in 65% of individuals with RTT syndrome (during their typical behaviour). However, hypothesis 2 (aim 2) was not supported as there was no significant difference in the prevalence of attenuated behaviour during 'typical' behaviour and during RE. This suggests that despite some similarities in the depiction of attenuated behaviour and RE, they do not co-occur and should be considered as separate and a distinct cluster of behaviours. With regard to the third aim, all of the attenuated

behaviour core symptoms were reported as present, with each core symptom being present in between 46-57% of the participants. The highest reported core symptom was 'requires prompts to complete action', which was consistent with findings in ASD, FXS and CdLS (Bell et al., 2018; Breen & Hare, 2017).

When testing hypothesis 3, a negative association with age was present in both the frequency and severity scores which, to date, appears to be RTT-specific. Given the regression of skills in individuals with RTT, it was considered probable that age would be more likely to be *positively* correlated with severity. Moreover, research into autistic catatonia (AB) and ASD suggests that age of onset is gradual and around 10-19 years (Wing & Shah 2000). One probable explanation for the negative correlation is that the individuals in the present study mainly fell within stage II (developmental regression) and stage III (pseudo stationary period with some degree of recovery). It is most likely that individuals at stage I would not have been diagnosed and individuals at stage IV would have not been able to fully complete the ABQ and thus their data would have been omitted. Therefore, the most severe scores would be during stage II which represents the 'regression' stage and the least severe scores would be during stage III. Motor abilities in younger girls have been found to have a higher decline in complex skills (after a four year follow up) than older age ranges of RTT (13 years plus) (Foley et al. 2011). Moreover, skills can be preserved or acquired following the regression stage (Foley et al. 2011). The findings support the hypotheses that there is an inverse U curve for skills in RTT. It could be also be hypothesised that parental distress would be higher and more alert during the earlier stages and later they might be more desensitised to changes.

In relation to aim 5, RTT was found to have the highest prevalence rates amongst other genetic conditions previously researched (CdLS, FXS and ASD). Research into autistic catatonia has found that individuals with greater language impairments are at higher risk of

developing autistic catatonia (Wing & Shah 2000). In light of this, it could be proposed that individuals with RTT have greater language impairments than the other genetic syndromes and thus are at increased risk of attenuated behaviours. It is unclear why a greater language impairment would place individuals at increased risk. One hypothesis could be that similar or related areas of the brain are impacted upon. Alternatively, the higher prevalence in RTT might reflect that the ABQ could hold low specificity within the RTT population.

Support for hypotheses 1, 2 & 3 notwithstanding, the current study has a number of limitations and the above preliminary results should be treated with caution. The most obvious limitation, common to many other studies of rare genetic syndromes, is that of small sample size. A further limitation that is more specific to the current study is reliance on parental self-report for both attenuated behaviours, mitigated to some degree by the use of the ABQ, and RE in the absence of a robust classification system for the latter. The use of video recordings of RE and coding by independent raters is therefore recommended for future studies, albeit that this would have significant implications in terms of both resources and the ethical acceptability of the research.

The sampling method used had the potential to skew the data, given the recruitment of families who had already agreed to be contacted for research purposes and who may therefore already be more motivated to assist in the development of future research and support for their child. This may in turn be influenced by the age of their child, the current phase and severity of their RTT symptomology or how well supported the parents feel. Longitudinal research has shown maternal well-being is predicted by their child's behavioural and emotional difficulties as opposed to the RTT behavioural phenotype (Cianfaglione et al. 2017). The relationship between perceived support and reporting of RTT symptomology has

not been researched. A measure of perceived familial support could be incorporated into future research projects.

Given the severe motor malfunctioning in the later stages of RTT, five of the participants were unable to complete all items of the ABQ and thus their results were omitted. This reflects the challenges of using a scale that is not 'disorder specific'. However given that attenuated behaviour research is in its infancy, no other options were available. In addition, it was imperative to use a consistent scale across different disorders. The ABQ is yet to establish inter-rater and test-retest reliability, which again may compromise the conclusions drawn from this research.

The rarity of the condition, the different stages of RTT and the inter-individual variability within RTT individuals makes it challenging to obtain a sample with consistent presentation. This again presents challenges in the generalisability of the results, however it is problematic to mitigate this given the lack of availability of a larger sample.

The 88% prevalence rate of RE found in this study is a slightly higher prevalence than that found in a previous study (Cardoza et al. 2011). The smaller sample size might have skewed the results and may account for the slight disparity in results. Alternatively, the higher prevalence rates may reflect the increased awareness of RE as a result of Cardoza et al's study (2011). The method of validating RE by specialised clinicians also presents challenges to the reliability and the ability to replicate the study. However, in the absence of a robust classification system, these limitations are not restricted to this study. The cross-sectional design of the current study does not allow for extraneous variables to be controlled for and

did not allow for attenuated behaviours to be measured across time points as it would in longitudinal research.

Implications for clinical practice

The results of the current study contribute to the emerging body of knowledge regarding attenuated behaviour across genetic neurodevelopmental disorders. The initial prevalence rates of 65% indicate that clinical attention to attenuated behaviours in RTT is appropriate and individuals with RTT are routinely assessed for the presence of attenuated behaviours. The reasons for this are, firstly, that individuals with RTT can use behaviours such as self-injurious hand functions as idiosyncratic communication functions (Oliver et al. 1993) and thus during periods of attenuated behaviours, such communication attempts may be further impeded. Attenuated behaviours may further reduce engagement in activity and mobility. Although information regarding non-medical interventions for RTT is still sparse, a recent review (Amoako & Hare *in preparation*) indicated that the majority of interventions focussed on communication.

Secondly, assessment of attenuated behaviours and recognition that these may form part of the behavioural phenotype, is clinically important not only to prevent inappropriate treatment, often in the form of anti-psychotic medication or ECT, but also to support the use of possibly ameliorative interventions developed for use with similar presentations in ASD (Hare & Malone 2004; DeJong et al. 2014). On this basis, when caring for individuals with RTT, familial and paid carers could assist them by providing them with physical and verbal prompts. Each individual's current functioning ought to be considered with care. Individuals who are experiencing a period of attenuated behaviour should not have increased demands on them, but maintenance of activities and external stimulation utilised. Comfort and support during

times of attenuated behaviour will minimise any associated distress. Functional analysis of the identification of stress factors (including environmental, lifestyle and psychological) should be completed to enable modification of such factors (Wing & Shah 2000).

Recommendations for Clinical Psychologists

The study highlights the prevalence of attenuated behaviour in RTT. The aetiology and function of attenuated behaviour in RTT is not yet understood. Now that prevalence has been established, Clinical Psychologists can lead on developing functional analyses to understand more about the aetiology and function within RTT and other genetic conditions. In addition, Clinical Psychology skills are well placed to facilitate learning of when attenuated behaviour is *not* present, or times at which attenuated might be increased or decreased. Clinical Psychologist skills in neuropsychology may assist in the understanding of attenuated behaviour and future research into attenuated behaviour.

Clinical Psychologists skills in research and dissemination of research makes them well placed to both develop further research projects into attenuated behaviour, but also facilitate learning of the prevalence of attenuated behaviour into clinical practice. This can be facilitated via training and consultation with clinical staff. In addition, their communication skills allow them to discuss and communicate to families and carers the role of attenuated behaviour.

Recommendations for future research

Research into AB and use of the ABQ is novel. Therefore it isn't clear if AB is a 'severe' problem. On the basis of this preliminary study AB in RTT appears to be higher than in other

genetic conditions and merits further investigation. This is the first study into AB in RTT, therefore further studies are needed into the behavioural phenotyping mapping of AB in RTT to investigate if AB is separate from RTT or if it could be part of RTT symptomology.

Based on the findings of this study, further research into attenuated behaviour profiles across related clinical presentations such as CDKL5 and FOXG1 is warranted. Future research could also focus on longitudinal studies to provide information of the trajectory of attenuated behaviours and the severity across the ages and stages of RTT and the specific genotypes. In addition, research into the impact of attenuated behaviours on individuals may contribute to our understanding of the specific challenges attenuated behaviour brings. Raising the profile of attenuated behaviours within genetic syndromes may assist in the development of practice-based evidence interventions for the treatment of attenuated behaviours. A further area to explore is attenuated behaviours in the context of a response lag. 'Response lag' is often commented on anecdotally by clinicians working in the field of RTT, and is described clinically as a longer than usual period of time that individuals with RTT will use to respond. This is an area that to date has not been researched.

Further research into the aetiology of attenuated behaviour in RTT is required. A variety of aetiological mechanisms have been proposed for catatonia / attenuated behaviour in ASD including GABA abnormalities (Dhossche & Rout 2006), trauma (Wing & Shah 2000) and tonic immobility as a response to anxiety (Moskowitz 2004). Similarly to that proposed with regard to ASD, there is preliminary research indicating that RTT is associated with elevated glutamate levels / reduced GABA levels (Johnston et al. 2015) as well as other neurotransmitter abnormalities including reduced dopaminergic activity.

Conclusions

This current study explored the prevalence of attenuated behaviours within RTT, the core symptoms within RTT and the prevalence during RE. Findings of this current study suggest that attenuated behaviour is present within the RTT. The results did not find an elevation of attenuated behaviours during RE. Attenuated behaviours as rated by the ABQ were found to be higher in RTT than in other neurodevelopmental conditions (ASD, CdLS and FXS). The results indicated that the severity of attenuated behaviours is negatively correlated with age. The research highlights the limitations of conducting research into rare conditions, which inevitably impact on sample sizes and the generalisability of the research. Further research is necessary to establish a greater understanding of the impact of attenuated behaviours within RTT syndrome specifically. In addition, research into interventions that might relieve attenuated behaviours across additional genetic syndromes will promote the understanding of this phenomenon.

References

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

Bebbington, A., Anderson, A., Ravine, D., Fyfe, S., Pineda, M., De Klerk, N., … Leonard, H. (2008). Investigating genotype-phenotype relationships in Rett syndrome using an international data set. *Neurology*, *70*(11), 868–875. http://doi.org/10.1212/01.wnl.0000304752.50773.ec

Bell, L., Oliver, C., Wittkowski, A., Moss, J., & Hare, D. (2018). Attenuated behaviour in Cornelia de Lange and fragile X syndromes. *Journal of Intellectual Disability Research*. http://doi.org/10.1111/jir.12481

Billstedt, E., Gillberg, C., & Gillberg, C. (2005). Autism after adolescence: Population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *Journal of Autism and Developmental Disorders*, *35*(3), 351–360. http://doi.org/10.1007/s10803-005-3302-5

Breen, J., & Hare, D. J. (2017). The nature and prevalence of catatonic symptoms in young people with autism. *Journal of Intellectual Disability Research*, *61*(6), 580–593. http://doi.org/10.1111/jir.12362

Cardoza, B., Clarke, A., Wilcox, J., Gibbon, F., Smith, P. E. M., Archer, H., … Kerr, M. (2011). Epilepsy in Rett syndrome: association between phenotype and genotype, and implications for practice. *Seizure : The Journal of the British Epilepsy Association*, *20*(8), 646–9. http://doi.org/10.1016/j.seizure.2011.06.010

Cass, H., Reilly, S., Owen, L., Wisbeach, A., Weekes, L., Slonims, V., … Charman, T. (2003). Findings from a multidisciplinary clinical case series of females with Rett syndrome. *Developmental Medicine and Child Neurology*, *45*(5), 325–337.

http://doi.org/10.1111/j.1469-8749.2003.tb00404.x

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

Cianfaglione, R., Hastings, R. P., Felce, D., Clarke, A., & Kerr, M. P. (2017). Change over a 16-month period in the psychological well-being of mothers of girls and women with Rett syndrome. *Developmental Neurorehabilitation*, *20*(5), 261–265. http://doi.org/10.3109/17518423.2016.1142483

Cohen, J. (1988). *Statistical Power Analysis for the Behavioural Sciences* (2nd Edition). Hillsdale, N. J. Lawrence Erlbaum.

Cooper, R. A., Kerr, A. M., & Amos, P. M. (1998). Rett syndrome: critical examination of clinical features, serial EEG and video-monitoring in understanding and management. *European Journal of Paediatric Neurology : EJPN : Official Journal of the European Paediatric Neurology Society*, *2*(3), 127–135. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10726834

Dhossche, D. M., & Rout, U. (2006). Are Autistic and Catatonic Regression Related? A Few Working Hypotheses Involving Gaba, Purkinje Cell Survival, Neurogenesis, and ECT. *International Review of Neurobiology*. http://doi.org/10.1016/S0074-7742(05)72004-3

Efron, B., & Tibshirani, R. (1994). *An introduction to the bootstrap*. Chapman & Hall. Retrieved from https://www.crcpress.com/An-Introduction-to-the-Bootstrap/Efron-Tibshirani/p/book/9780412042317

Faul, F., Erdfelder, E., Lang, A., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioural, and biomedical scieneces. *Behavior Research Methods*, 39(2), 175-131. http://doi.org/10.3758/bf03193146.

Field, A. (2013). Discovering Statistics using IBM SPSS Statistics. *Discovering Statistics Using IBM SPSS Statistics*, 297–321. http://doi.org/10.1016/B978-012691360-6/50012-4

Filloux, F. M., Carey, J. C., Krantz, I. D., Ekstrand, J. J., & Candee, M. S. (2012). Occurrence and clinical features of epileptic and non-epileptic paroxysmal events in five children with Pallister-Killian syndrome. *European Journal of Medical Genetics*, *55*(5), 367–373. http://doi.org/10.1016/j.ejmg.2012.01.006

Foley, K.-R., Downs, J., Bebbington, A., Jacoby, P., Girdler, S., Kaufmann, W. E., & Leonard, H. (n.d.). Change in Gross Motor Abilities of Girls and Women With Rett Syndrome Over a 3-to 4-Year Period. http://doi.org/10.1177/0883073811402688

Ghaziuddin, M., Quinlan, P., & Ghaziuddin, N. (2005). Catatonia in autism: A distinct subtype? *Journal of Intellectual Disability Research*, *49*(1), 102–105. http://doi.org/10.1111/j.1365-2788.2005.00666.x

Glaze, D. G., Schultz, R. J., & Frost, J. D. (1998). Rett syndrome: Characterization of seizures versus non-seizures. *Electroencephalography and Clinical Neurophysiology*, *106*, 79–83. http://doi.org/10.1016/S0013-4694(97)00084-9

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

Hagberg, B., Aicardi, J., Dias, K., & Ramos, O. (1983). A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: Report of 35 cases. *Annals of Neurology*, *14*(4), 471–479. http://doi.org/10.1002/ana.410140412

Hagberg, B., Witt-Engerström, I., Opitz, J. M., & Reynolds, J. F. (1986). Rett Syndrome: A suggested staging system for describing impairment profile with increasing age towards adolescence. *American Journal of Medical Genetics*, *25*(S1), 47–59. http://doi.org/10.1002/ajmg.1320250506

Hagne, I., Witt-Engerstrom, I., & Hagberg, B. (1989). EEG development in Rett syndrome. A study of 30 cases. *Electroencephalogr Clin Neurophysiol*, *72*(1), 1–6.

Hare, D. J., & Malone, C. (2004). Catatonia and autistic spectrum disorders. *Autism : The International Journal of Research and Practice*, *8*(2), 183–195. http://doi.org/10.1177/1362361304042722

Jian, L., Nagarajan, L., de Klerk, N., Ravine, D., Christodoulou, J., & Leonard, H. (2007). Seizures in Rett syndrome: An overview from a one-year calendar study. *European Journal of Paediatric Neurology*, *11*(5), 310–317. http://doi.org/10.1016/j.ejpn.2007.02.008

Johnston, M., Blue, M. E., & Naidu, S. (2015). Recent advances in understanding synaptic abnormalities in Rett syndrome. *F1000Research*. http://doi.org/10.12688/f1000research.6987.1

Julu, P. O., Engerström, I. W., Hansen, S., Apartopoulos, F., Engerström, B., Pini, G., … Smeets, E. E. (2008). Cardiorespiratory challenges in Rett's syndrome. *The Lancet*, *371*(9629), 1981–1983. http://doi.org/10.1016/S0140-6736(08)60849-1

Kim, H. L., Donnelly, J. H., Tournay, A. E., Book, T. M., & Filipek, P. (2006). Absence of seizures despite high prevalence of epileptiform EEG abnormalities in children with autism monitored in a tertiary care center. *Epilepsia*, *47*(2), 394–398. http://doi.org/10.1111/j.1528-1167.2006.00434.x

Mackay, J., Downs, J., Wong, K., Heyworth, J., Epstein, A., & Leonard, H. (2017). Autonomic breathing abnormalities in Rett syndrome: caregiver perspectives in an international database study. *Journal of Neurodevelopmental Disorders*, *9*(1), 15. http://doi.org/10.1186/s11689-017-9196-7

Moskowitz, A. K. (2004). "Scared stiff": Catatonia as an evolutionary-based fear response. *Psychological Review*. http://doi.org/10.1037/0033-295X.111.4.984

Neul, J. L., Fang, P., Barrish, J., Lane, J., Caeg, E. B., Smith, E. O., … Glaze, D. G. (2008).

Specific mutations in Methyl-CpG-Binding Protein 2 confer different severity in Rett syndrome. *Neurology*, *70*(16), 1313–1321. http://doi.org/10.1212/01.wnl.0000291011.54508.aa

Neul, J. L., Kaufmann, W. E., Glaze, D. G., Christodoulou, J., Clarke, A. J., Bahi-Buisson, N., … Percy, A. K. (2010). Rett syndrome: Revised diagnostic criteria and nomenclature. *Annals of Neurology*, *68*(6), 944–950. http://doi.org/10.1002/ana.22124

Oliver, C., Murphy, G., Crayton, L., & Corbett, J. (1993). Self-injurious behavior in Rett syndrome: interactions between features of Rett syndrome and operant conditioning. *Journal of Autism and Developmental Disorders*, *23*(1), 91–109. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8463204

Parmeggiani, A., Barcia, G., Posar, A., Raimondi, E., Santucci, M., & Scaduto, M. C. (2010). Epilepsy and EEG paroxysmal abnormalities in autism spectrum disorders. *Brain and Development*, *32*(9), 783–789. http://doi.org/10.1016/j.braindev.2010.07.003

Realmuto, G. M., & August, G. J. (1991). Catatonia in autistic disorder: a sign of comorbidity or variable expression? *Journal of Autism and Developmental Disorders*, *21*(4), 517–28. http://doi.org/10.1007/BF02206874

Reilly, S., & Cass, H. (2001). Growth and nutrition in Rett syndrome. *Disability and Rehabilitation*, *23*, 118–128.

Steffenburg, U., Hagberg, G., & Hagberg, B. (2001). Epilepsy in a representative series of Rett syndrome. *Acta Paediatrica, International Journal of Paediatrics*, *90*(1), 34–39. http://doi.org/10.1080/080352501750064842

Williams, J., & MacKinnon, D. P. (2008). Resampling and distribution of the product methods for testing indirect effects in complex models. *Structural Equation Modeling*, *15*(1), 23–51. http://doi.org/10.1080/10705510701758166

Wing, L., & Shah, A. (2000). Catatonia in autistic spectrum disorders. *The British Journal of*

Psychiatry : The Journal of Mental Science, *176*, 357–362. http://doi.org/10.1192/bjp.176.4.357

Witt Engerstrom, I. (1990). Rett syndrome in Sweden. Neurodevelopment-disability-pathophysiology. *Acta Paediatrica Scandinavica. Supplement*, *369*, 1–60. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1701067

Witt Engerstrom, I. (1992). Age-related occurrence of signs and symptoms in the Rett syndrome. *Brain & Development*, *14 Suppl*, S11–S20. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=1378244

Young, D., Nagarajan, L., de Klerk, N., Jacoby, P., Ellaway, C., & Leonard, H. (2007). Sleep problems in Rett syndrome. *Brain and Development*, *29*(10), 609–616. http://doi.org/10.1016/j.braindev.2007.04.001

Paper 3

A reflective paper on the process of completing papers

1 & 2.

Word Count 7899

Introduction

This paper offers a reflective critique of the research process for the submitted thesis. It critically appraises the research across the systematic review and the empirical study at all stages of the research process. The appraisal discusses the strengths and limitations of the research and key reflections on decisions taken. The following paper further includes detailed information regarding the processes and planning of the thesis, that were not able to be captured within the author guidelines of the proposed journal submissions.

Appraisal of Systematic Literature review

Research Context

In the early stages of planning the systematic review, consideration was given to conducting a systematic review into attenuated behaviours (catatonic autism) with the aim of improving consistency between the thesis papers. Regrettably however, a 2014 systematic review into autistic catatonia interventions had already been completed (DeJong, Bunton, & Hare, 2014). Moreover, given that DeJong et al highlighted the lack of high quality papers in this area and therefore a paucity of research into attenuated behaviours it was felt there was no rationale for completing a further review into attenuated behaviours at this stage. Further consideration was given to conducting a review into the behavioural phenotypes of Rett Syndrome (RTT) (again to aid consistency between the two papers), however again recent local research into RTT phenotypes (Cianfaglione, Clarke, Kerr, Hastings, Oliver, & Felce, 2015a; Cianfaglione,

Clarke, Kerr, Hastings, Oliver, Moss, et al., 2015) had been completed and therefore it was felt a systematic review paper would not add to the body of knowledge already existing.

The author's experience of working with individuals with profound and severe disabilities resulted in a passion and enthusiasm for improving the quality of life for individuals with RTT via clinical interventions. Currently working with individuals with genetic syndromes such as RTT presents challenges for clinicians. There is a lack of clear guidelines and few dedicated services for these individuals. Fortunately, in Wales there is the All Wales Genetics Centre who offer Rett Clinics for individuals, providing advice and support. However, the clinics are biannual and therefore there are pressures on how much assistance can be provided to individuals, their families and clinicians. Within local services, individuals with severe and profound difficulties such as RTT are typically referred to Clinical Psychologists at times of transition or when the individual is displaying behaviour that challenges such as self-injurious behaviour. The role of Clinical Psychology typically takes on a consultancy / training model aimed at enabling care staff to manage specific behaviours or provide time limited interventions. The author recognised that when working in intellectual disability services, clinicians often work within a generic model for severe and profound disabilities and lack direct clinical guidance for each genetic condition – this ignores the complexity and wide-ranging variance between developmental disorders. To date, the only systematic reviews into RTT interventions had specifically researched communication interventions (Sigafoos et al., 2009) and communication assessment (Sigafoos et al., 2011).

The author chose to conduct an inclusive systematic review which investigated all types of interventions and incorporated recent literature. The author chose to exclude medical

interventions, firstly due to the brevity of potential medical interventions for RTT which might be outside the authors' area of expertise. Secondly, it was felt that non-medical interventions were largely under-represented within the literature and therefore a review of the literature would allow for an increased profile of the importance of non-medical interventions.

This systematic review is extremely timely in its presentation. There have been several recent advances into the use non-medication interventions within the scope of intellectual disabilities such as the use of 'high technology' Assistive Technologies (AT) (Borgestig, Sandqvist, Parsons, Falkmer, & Hemmingsson, 2016; Perelmutter, McGregor, & Gordon, 2017). More recently these high technology AT have been trialled in the RTT population (Lancioni et al. 2008;). Given the vast challenges in communication for individuals with RTT, it is imperative that clinicians can support evidenced based interventions to assist in the communication and quality of life for such individuals.

In addition to the advances in AT, this study is also very timely given there are recent movements within the RTT community to re-evaluate the conceptualisation of cognitive abilities within RTT. Historically, accurate systematic assessments and evaluations of individuals with RTT's cognitive ability had not been achieved due to the severe commination impairments they present with (Neul et al., 2010), nevertheless individuals with RTT were considered to fall within the severe to profound categorisation of intellectual disability. In recent years there have been international movements to understand more about the levels of cognition in RTT. Parents have often reported that they feel their children have a greater understanding of language than clinicians predict. They have described their children using communication skills such as eye pointing to communicate their language comprehension and

skills. Individuals with RTT have been found to be more intellectually capable than they present as (Djukic, Valicenti McDermott, Mavrommatis, & Martins, 2012; Rose et al., 2013). This is because the challenges in their *ability* to communicate can mimic deficits in cognitive ability.

Advances in augmentative and alternative communication (AAC) devices have assisted individuals with their communication skills and as such have found that children's cognitive abilities are not as profound as typically suggested. Ahonniska-Assa et al. (2018) found 32% of the participants ranged from low-average to mild cognitive impairment. The exact extent of cognitive abilities in RTT remains largely unknown. However, such advances in understanding the cognitive abilities in individuals with RTT can assist the development of further research into communication strategies which are better matched to cognitive abilities.

Successful communication interventions will assist firstly in the knowledge base of communication strategies and secondly assist in the development of cognitive phenotypes in RTT. However, most importantly successful interventions will assist individuals with RTT to communicate their needs, thoughts and feelings. In light of this, it is imperative that clinicians working with individuals with RTT are able to access a review which directs them to interventions that they can use in their clinical practice and in doing so improve the quality of life of individuals with RTT.

As such, the author hoped that improving the evidence base behind non-medical interventions in RTT, might inform the consultancy and training role played by clinical psychologists, as well

as their own clinical practice. The secondary aim would be that such a review would be beneficial for multidisciplinary clinical staff in both their clinical practice.

An additional motivation for completing this study was to utilise the skills of Clinical Psychology within a systematic review process. It was recognised that many of the studies of RTT interventions had been completed by very passionate Occupational Therapists, Physiotherapists and Speech and Language Therapists. These individuals were very skilled and experienced within their field of work, and had worked hard to publish and disseminate their research into interventions for RTT alongside their clinical duties. However a scope of the literature indicated some of these studies may benefit from more vigorous research process. Therefore this review would firstly assist in emphasising the higher quality research into RTT interventions but hopefully it would also highlight and model the methodological changes that could be made to improve the research vigour of future studies.

As well as raising awareness of research quality improvement, the author aimed to assist in providing an increased psychological presence and theory within genetic syndromes such as RTT. Given the profound communication, physical and functional limitations of individuals with RTT, it was surprising that there was such a paucity of research into interventions by Clinical Psychologists. Therefore the research aimed to assist in the development of Clinical Psychology within the field of RTT.

Methodology

Research Design

Ideally a meta-analysis would have been conducted to enable a calculation of effect size. A meta-analysis was not conducted due to the variation in the variables, designs and outcome measures of the studies (Garg, Hackam, & Tonelli, 2008). A systematic review was selected to ensure that standardised, replicable and inclusive review of the literature could be achieved. The aim of the systematic review was to present a clear and concise review of the good quality interventions, in order to be a useful resource for clinicians working with RTT.

Search terms and inclusion criteria

The search terms were cross referenced with previous reviews and studies into RTT (Sigafoos et al. 2009; Sigafoos et al. 2011; Cianfaglione et al. 2015) to check if any additional terms were required. Given the dearth of literature into interventions for individuals with RTT the yield of search results was not unmanageable to systematically select relevant non-medical studies. Therefore using broad terms was appropriate to incorporate as many relevant studies as possible. The strengths of this is that the research is more inclusive. Furthermore, the research is less likely to be influenced by the author's values and professional background affecting choice of terminology. For example as the author works within clinical psychology field, they could have inadvertently been influenced to research 'psychological interventions'

or ‘communication interventions’. However, including more diverse range of interventions has resulted in the review being harder to draw consistent conclusions.

Given the focus of this review was to capture a brevity of research, the articles were not restricted to date ranges. Articles were included if they were available in English and available as full text articles. Only non-medical interventions were excluded. The review followed best practice for systematic reviews by restricting the articles to published, peer reviewed articles (Jesson, Matheson, & Lacey, 2011). Whilst this may have limited the potential for conference abstracts and unpublished theses, it was decided that this would increase the research vigour of the review.

Upon reflection, articles could have been missed if they have researched trans-diagnostic populations / interventions and as a result, they did not include RTT specifically in the search terms. An example of this would be if the intervention was inclusive of individuals with severe and profound intellectual disabilities and as such included different genetic conditions. Ideally such articles would include RTT in the search terms, so they would have been captured. A further difficulty arose in being able to capture assistive technology articles which often do not include intervention in the title. For example, they may have included the specific types of assistive technologies like ‘*eye gaze technology*’ or ‘*microswitch technology*’. In light of the fact that there is a vast range of potential types of assistive technologies that would be included in the title it would not be possible to include all of these search terms, however it was noted the search did yield a number of assistive technologies where intervention was not in the title. A retrospective search using the search terms ‘eye-gaze technology’ and ‘assistive technology’

did not terms did not yield any additional results, because they included 'interventions' in their key words.

Quality Assessment

A quality assessment checklist was enlisted to enable a high degree of transparency and control for potential biases. The studies required a quality assessment checklist that was validated for case series and case studies. Boland et al (2014) recommended the use of a single case quality measure used in the medical literature (Cowley, 1995). However this quality assessment would have required modification. Alternative quality appraisal tools for case series were considered (Vere & Joshi, 2012; Yang et al., 2009; Young, Fry-Smith, & Hyde, 1999), however these quality checklists had not been validated and were developed around specific conditions.

The Quality Appraisal Tool for Case Series (Moga et al. 2012) was selected because it has been specifically developed for case series using a rigorous research process using a modified Delphi technique. In addition, a review of quality measures (Zeng et al., 2015) recommended the use this measure. Thus, this 20 item tool was deemed the most appropriate measure to assess the methodological quality of case series. The checklist includes items relating to study objective, intervention co-intervention, outcome measure, statistical analysis, results and conclusions and competing interests. In choosing a case study and case series quality measure, the author considered developing their own measure. However, on balance the author opted to use a measure that has previously been used and developed using a rigorous research process.

The Quality Appraisal Tool is designed to be tailored to specific reviews (Guo, Moga, Harstall, & Schopflocher, 2016). In light of this the tool was modified to reflect the most relevant and important clinical aspects. Five items were omitted; multicentre study (item 3), consecutive recruitment (item 4), co-intervention description (item 9), losses (item 16) and participants entering at similar points in their disease (item 7). It was thought that the nature of researching rare genetic syndromes such as RTT would mean that such items would not be achieved because of the small n numbers of recruitment.

The tool does not provide numerical scoring and items are scored via a yes, no, unclear or partial. However, systematic reviews have assigned 1 point for a yes and half a point for unclear or partial responses (Auger, Hernando, & Galmiche, 2017; Roland, Skillington, & Ogden, 2017). To ensure that the review focused on studies with an adequate methodological quality, the scoring criteria set by Auger et al (2017) was adopted. Thus, a score above 14 was deemed to have adequate methodological level. However as The Quality Assessment Tool for Case Series is continuing to undergo a validation process, the application of the tool needs to be interpreted cautiously.

Systematic Review Process

Prior to the review being conducted a systematic review protocol was constructed. To assist in the development of the review protocol, the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statements (Moher D, A, & Tetzlaff J, 2009) were referenced and Boland et al's (2014) guidelines were followed. The PRISMA checklist and

diagram assisted in both the record keeping of the articles and the standardisation of the review process.

Quality assessment tools can be vulnerable to bias and inter-rater reliability (Higgins et al., 2011). A second reviewer of the quality scores was used to assist in reducing bias. Ideally the second reviewer would have rated all articles, however resources would not allow for this as part of the Doctoral thesis. To reduce bias and increase inter-rater reliability 20% of the studies were reviewed by a second reviewer (Higgins et al., 2011).There was moderate inter-rater reliability. Upon review, the author noted that differences were mainly concerned with where one rater scored unclear / partial and the other rater scored yes or no. These differences might have been due to the raters' different thresholds for rating and the difficulties in subjectivity and clarification in the criteria of what constituted a partial or a yes or no. For example on more subjective questions such as 'was the intervention of interest clearly described?' or 'were the aims of hypothesis clearly stated?'. Ratings were more consistent on items such as 'was the study conducted prospectively' or 'were the characteristics of the patient in the study clearly described?'.

Systematic Review Findings and Conclusions

The main findings are summarised in Paper 1, therefore they will not be repeated within this paper. Additional clinical implications and research implications will be summarised.

Participant recruitment

The systematic review incorporated national and international research. However, the author noted a trend that UK intervention studies were very sparse and typically involved small N number research in comparison to international studies. The reasons for this can be hypothesised. Firstly, the review highlighted that larger participant numbers were drawn from countries that collaborated with a National Rett association. Whilst the UK does have a Rett Association, the funding for the research database administrator was ceased and as such, the UK research database is no longer actively maintained. This has resulted in challenges in the accuracy of contact details and as such the recruitment on future studies (see chapter 2). Secondly, individuals with RTT are typically seen within intellectual disability services across the UK, as such, it would be unlikely for a clinical team to have a large recruitment pool. The potential to obtain NHS ethics across different health boards / trusts is challenging. Therefore, future recruitment would be best sourced by linking in with International Associations.

Clinical and Research Implications

The nature of RTT means that individuals are characterised by their inability to use speech and make hand gestures thus leading to severe and enduring challenges in their ability to communicate their needs. In addition to these challenges, individuals with RTT are often further debilitated by additional secondary challenges such as; isolation, impaired mobility and general low quality of life (Felce & Perry, 1995; Gutowski, 1996; Ivancic & Bailey, 1996; Parisi,

Filippo, & Roccella, 2016). The nature of these challenges means it is imperative that clinical practice focuses on interventions to improve them. This systematic review highlighted that utilising non-medical interventions which are tailored to the individual will improve both target behaviours but also secondary behaviours. There is no evidence that these interventions have caused damage or distress, therefore in terms of future clinical practice such interventions could be trialled or adapted to individuals with RTT.

Ideally future research would include larger sample sizes. However the nature and trajectory of the genetic phenotype of RTT means that there will always be clinical variation depending on the stage of the individual. Individuals will inevitably be at different developmental stages and additional co-morbid physical health concerns will be present. Therefore, it will always be inevitably challenging to draw firm research conclusions because even within the same genetic phenotype (RTT) they will be to an extent a heterogeneous group. Even in circumstances where one variable is matched, e.g stage of Rett and age, the results of the studies would be compromised to a degree, due to potential external variables such as medication, Rett episodes, environment, staffing. In light of this, case study research might be a more realistic reflection of clinical recommendations. It is imperative that practice based evidence is encouraged by clinicians. Clinical Psychologists working in intellectual disability services have a role to offer multidisciplinary professionals who are not research trained. For example, they can assist professionals to firstly conduct practice-based research, secondly to increase the research vigour of small case studies and thirdly assist them in publishing and disseminating their research. This is an area of which the author is keen to take forward personally, in their future development.

Appraisal of Empirical Paper

Research Context

This empirical study into specific attenuated behaviour phenotypes is very timely in its presentation. Recent research conducted at Manchester University has found a prevalence of attenuated behaviours in Cornia de lange (CdLS), Fragile X Syndrome (FXS) and Autism Spectrum Disorder (Bell, Oliver, Wittkowski, Moss, & Hare, 2018; Breen & Hare, 2017). The emergence of this research has raised the importance of screening for attenuated behaviour in the aforementioned conditions. The research additionally highlighted that attenuated behaviour may be present in additional syndromes / disorders. Given movement abnormalities are a predominant feature in RTT, it was queried if individuals with RTT may also experience symptomology of attenuated behaviour.

Development of research question

A meeting was arranged with RTT specialists to discuss initial research ideas. The emergence of a research hypotheses was discussed. Clinical expertise indicated that attenuated behaviour might be present in RTT. It was proposed however that there may be a clinical cross-over or relationship with 'Rett Episodes' (RE) and attenuated behaviour. To date, the research into RE is very limited (Weaving, Ellaway, Gécz, & Christodoulou, 2005) and as such requires further investigation. Whilst there have been attempts to classify it behaviourally (Glaze, Schultz, & Frost, 1998), it is acknowledged clinically that the criteria is broad and there might

be different 'types' of RE. Therefore any further understanding of RE as well as any potential link to research in attenuated behaviours would be a useful contribution to the research.

Methodology

Selecting suitable measures in behavioural phenotype research is challenging. Syndrome specific questionnaires are often not developed and those that are often hold reduced validity but do allow for the questionnaires to be tailored to the syndrome specific behaviours (Flint, 1996). This research used both a tailored syndrome specific questionnaire (REQ) and a non-syndrome specific questionnaire (ABQ).

Measures

Rett Episodes Questionnaire (REQ) and Validation

As described previously, currently there is not an empirical test or classification of RE. Therefore it was felt that the most appropriate way to ensure the classification of the descriptions provided would be to consult with a specialist in the area of RTT (Dr Angus Clarke). This was in line with previous research into RE (Cardoza et al., 2011). The REQ was co-constructed with the input from Dr Clake. The results of the questionnaire was given to Dr Clarke and he reported if he felt the descriptions would be classified as RTT within the context of a Specialist Rett Clinic. In the absence of a more robust classification system or

test, this was felt to be the most suitable way ensure RE were correctly identified. However the author recognised that this leads the study vulnerable to biases and compromised the ability to standardised and replicate the study.

Attenuated Behaviours Questionnaire (ABQ)

There is currently only one questionnaire for attenuated behaviours. The ABQ was originally derived from research into autistic catatonia. As such, the scale was originally named the Autistic Catatonia Questionnaire. However the developers of the Autistic Catatonia Questionnaire, revised the name to attenuated behaviours. This was amended to reflect the presence of autistic catatonia (attenuated behaviours) across different syndromes. In terms of autistic catatonia, catatonic type states had previously been identified in both neurological conditions and ASD (Patterson, 1986). The ABQ was developed using the clinical information derived from previous research (Hare & Malone, 2004; Wing & Shah, 2000). The questionnaire benefits from operationalised behavioural descriptions of catatonic type symptomology.

The author recognises that the ABQ is not validated within the RTT population. In the absence of a validated questionnaire into RTT, it was felt this was the most appropriate measure to use given it has good sensitivity (0.65) and specificity (0.38) (Breen & Hare, 2017).

The author sought to use the same analysis of the ABQ as used in previous affiliated studies (Bell et al., 2018; Breen & Hare, 2017). The limitations of this approach is that the only the ABQ core scores are used in the analyses and therefore this results in unused data. Initially, the author felt that using the ABQ in its complete format would also be beneficial for

exploratory analyses on the data at a later stage, in particular regard to the phenotyping of specific attenuated behaviours of RTT in comparison to earlier studies using the ABQ.

Whilst the ABQ is not overly timely to complete, it could be that removing the supplementary scoring for the ABQ, may have increased participation and dropout rates on the online questionnaire. In addition, there are ethical questions regarding collating additional data from participants if that data will not be used. Therefore, in hindsight, the author would have chosen to use the core questions for the ABQ.

One potential limitation with the ABQ is that, for participants who have profoundly impaired motor abilities (likely to be in Stage IV of RTT) some of the items are redundant. As a result of this a few participants omitted some items and commented alongside it if the question exceeded their child's motor ability. The ABQ was originally validated within an ASD population, in which motor abilities would not be impaired. However, when using the ABQ for more profound syndromes such as RTT and Cornelia de Lange Syndrome, the ABQ would benefit from having an additional option for such instances. The participants who completed the postal (paper) research pack, often noted next to the box that their child was not able to complete the action due to their impaired mobility. However, the online questionnaires did not have this capacity. The author feels the project would have benefitted from an 'opt out' or 'more information' box to account for this.

Additional questionnaire consideration and rationale

The author initially hoped to investigate repetitive behaviours alongside attenuated behaviour for the purpose of continuity with previous research into attenuated behaviours (Bell et al., 2018; Breen & Hare, 2017). The aforementioned research had revealed a relationship between repetitive behaviours (using the Repetitive Behaviour Questionnaire) and attenuated behaviour (Bell et al., 2018) with repetitive behaviours as a risk factor for attenuated behaviours. However the custodians of the research database used as the primary recruitment stream for present study had been approached as part of recent research to complete the Repetitive Behaviour Questionnaire (Cianfaglione, Clarke, Kerr, Hastings, Oliver, Moss, et al., 2015). Therefore the author felt it was not ethical to ask the same participants to complete the questionnaire again within a short time frame.

Review of measures

The challenges and limitations to the self-report measure are outlined in the empirical paper. An alternative method of conducting this research would have been to use observational scales of attenuated behaviour instead of parental self-report. However, this would not have been achievable due to the amount of resources it would require. In addition, the sample size would be likely to be reduced significantly.

The study design opted to utilise postal questionnaires (including self-return envelopes) as opposed to conducting the questionnaire face to face or via telephone. This was chosen to increase participant numbers and reduce the demands on the participants. A limitation of

using postal questionnaires was that some of the items were missing data without a reason and as such were not included. The reasons for this were unknown. In hindsight, the author would have included following up on such data in their protocol and ethics procedure.

Design

The study design was counter balanced, in to control for order effects. This meant that the two questionnaires for attenuated behaviour (ABQ) were given in different orders for participants to complete for RE and Non-Rett Episodes. Consideration was given to using a matched contrast group however it was felt that given the specific nature of RTT, their comorbid conditions and range of levels of functioning it would not be possible to accurately match the groups.

Recruitment and sample

Agreement and consent was sought to recruit from a research database, which was collated via the British Isles RTT Society. The database was held by an individual through Cardiff University and had recently recruited to a portfolio of research studies (Cianfaglione, Clarke, Kerr, Hastings, Oliver, & Felce, 2015a; Cianfaglione, Clarke, Kerr, Hastings, Oliver, Moss, et al., 2015; Cianfaglione, Hastings, Felce, Clarke, & Kerr, 2015).The previous studies had yielded between 87-91 carers of individuals with RTT. The present research contacted the same number of individuals using similar recruitment methodology. Effect size was considered,

however given there was not a comparable study to compute effect size, the sample size was estimated on previous studies to be N=75.

The research database had previously received funding and was updated regularly. However changes in funding had led to the database to have not been maintained within the past few years. After seeking consent, it was agreed this study could recruit via the database on the proviso that only parents who had previously had contact via Cianfaglione's studies (2015a, 2015b, 2015c) prior portfolio studies would be contacted and participants would not be contacted for a second reminder to participate in the programme. This was due to concerns about the database not being maintained and thus there being a risk of a significant time lapse between individuals consenting to be contacted for future studies and the potential for several address changes. There were also concerns that contacting individuals after several years might be distressing if their child's health had significantly deteriorated during a longer time frame or the child was now deceased. The original database held >900 parents and carers. However only N=290 were on the database and recorded as having contact with Cianfaglione's researchers' previously and therefore contacted for consent to this study.

The study further sought online recruitment via Rett UK using social media and a newsletter. This initial recruitment phase yielded only N=24 (8.3%) with online recruitment an additional N=4. Amendments to the recruitment processes were sought and approval was granted [Appendix 15]. Additional recruitment was sought via three online social media support groups for parents caring for individuals with RTT. In addition five international Associations for RTT were contacted to seek online consent and assistance for recruitment. Of the five

international charities contacted, one association replied and agreed for a social media posting of the online links to recruitment. The combination of these yielded an additional N=7.

Review of recruitment

The very nature of RTT being a rare genetic condition indicated that recruitment will be challenging and limited. It was hoped that that recruitment stream from the research database would be of similar numbers to the previous portfolio research (n70-90) (Cianfaglione, Clarke, Kerr, Hastings, Oliver, & Felce, 2015b; Cianfaglione, Clarke, Kerr, Hastings, Oliver, Moss, et al., 2015; Cianfaglione, Hastings, Felce, Clarke, & Kerr, 2017; Cianfaglione, Hastings, et al., 2015). However unfortunately the numbers were significantly less. It is thought that the main reason for this is the lack of ongoing upkeep and maintenance of the database. Many of the research envelopes were returned to the author because the recipient had moved address and there was not a forwarding address mentioned. In addition, the aforesaid studies required an extensive amount of data being collated. Therefore it could be hypothesised that potential participants experienced research fatigue from the previous project and did not participate because of this. The previous studies were able to phone individuals and post follow up reminders for participation of the research. The current study was granted permission to use the research database on the proviso that potential participants would be contacted via a postal method on one occasion.

It was thought that establishing online recruitment resources would enable increased access to participants and increase allow the study to be more accessible to complete. However, the online recruitment did not produce significant participants. It was noted that several participants commenced the online survey but did not complete the survey. This might reflect

that participants started the survey and found it too long to complete, or it might reflect the way in which individuals use social media - for example looking impulsively on their phones during short breaks. The challenges in online recruitment may also reflect that completing research does not meet the needs of the group members. Whilst the admins of the social media groups all agreed for details of the research project to be posted, it was evident that the group members either used the groups for emotional and psychological support from peers or used it to ask practical and sensitive health questions about their offspring.

After the initial period of recruitment (seven months), an addendum to the ethics committee was sought in the hope of increasing participant numbers. It was hoped that using online support forums and linking up with international organisations would assist in the recruitment. However this did not impact the sample size significantly.

The sample size is a major limitation in this study, however the author sought numerous recruitment avenues. The researchers felt all avenues for recruitment were exhausted and is likely to reflect the challenging nature of recruiting in rare genetic conditions, especially when the research is not embedded within a particular service. In the absence of an updated and maintained database, it is likely that challenges in recruitment will continue.

Data and statistical analyses

The Shapiro-Wilk test was used to test for normality of data for continuous variables and if parametric assumptions were not met, non-parametric analyses were conducted. Bootstrapping allowed for an estimate of the properties of the sampling distribution by treating the sample data as population data (Efron & Tibshirani, 1994; Field, 2013). The process was repeated 2,000 times. This allowed for a higher statistical power than other resampling approaches for small sample sizes. (Williams & MacKinnon, 2008). Dichotomous variables were tested using a McNemars test and Pearsons correlation co-efficient was computed when data met parametric assumptions to examine the relationship between variables.

The Shapiro-wilk test was used to test for normality of data on continuous variables. When parametric assumptions were met a paired t-test was used. If they were not met The Wilcox signed rank test was conducted on continuous variables that were non parametric (frequency of core symptoms). Whereas a paired t-test with bootstrapping was conducted on parametric continuous variables (severity scores). Dichotomous variables were tested using a McNemars Test (presence of AB above cut off). A Pearsons Correlation Coefficient was used when data met parametric assumptions to examine the relationship between variables (attenuated behaviour and age).

Clinical Implications

A strength of this empirical paper is its investigations into attenuated behaviour in RTT. To date, attenuated behaviour has not been reviewed in an empirical manner within RTT. The paper will assist clinicians in being aware of and screening for attenuated behaviour in RTT. In addition, the recognition of attenuated behaviour in RTT, introduces the prospect of future

research into attenuated behaviour phenotypes across genetic syndromes. The recognition of attenuated behaviours may be helpful for geneticists and other specialties working with RTT.

This study adds to the evidence-base of behavioural phenotypes of genetic disorders (namely RTT). Conducting research into behavioural phenotypes assists in raising awareness and thus education of specific behavioural phenotypes. In addition, it facilitates collaboration of research between multidisciplinary researchers. To date, it is often those syndromes with the highest prevalence rates that receive greater funding and attention (Dykens, 1995). Therefore this research assists in raising the profile and understanding of the behavioural phenotypes of RTT. Behavioural phenotype research has led the way in exposing relationships across genetic syndromes and understanding how individuals with genetic syndromes interact with their environment and how to modify their environment (Waite et al., 2014). In addition, behavioural phenotyping has been beneficial into understanding relationships such as between pain and self-injurious behaviour and / or aggressive behaviour for individuals with severe to profound intellectual disabilities (Waite et al., 2014).

In hindsight, the author feels that the study would have benefitted from gathering information about the participant's children's functional and motor ability. It would have been of particular interest to have clarified the Rett Stage of the children - given that they follow a unique trajectory for RTT. The stage of RTT would have been beneficial to clarify the utility of the ABQ within this population and potential false positives and / or limitations of the ABQ. This would be of particular relevance for Stage IV. Stage IV is the late motor deterioration stage. This is characterised by muscle weakness, stiffness, spasticity (uncontrolled muscle activity), dystonia (increased muscle tone), and scoliosis. This stage can last between years and decades.

Given the focus on motor movement in attenuated behaviour, caution must be given to the interpretation of the results for individuals who are in Stage IV.

Overall thesis project

The research project as a whole will contribute to the limited body of evidence of non-medicalised literature into RTT. The clinical and research implications have been summarised in the main papers. The author has been surprised by the under-representation of clinical psychology within this field. The role of clinical psychology within syndromes such as RTT are largely neglected, with the core professions often being medical professions (such as neurologist, geneticist, epileptologist, gastroenterologist and orthopaedic surgeon), social workers and therapists such as OTs and physiotherapists (Tarquinio & Percy, 2016).

This theses project has opened up discussions between multi-disciplinary experts in the field. As a result of this, future projects and collaborations are in the planning stage. Hopefully this will assist in future research projects utilising the skills of clinical psychologists as opposed to purely medical interventions and genetic investigations. For example, the combination of both papers has led to discussions around the concept of 'response lag' in individuals with RT. Anecdotally, parents and clinicians have indicated that individuals with RTT experience a response lag. This might form a similar presentation to attenuated behaviour, but furthermore, the response lag might not have been accounted for in some of the intervention studies. Currently, this is a concept that has not been researched, but is an area for further development within RTT.

A further role of for clinical psychologist in research is to combine their skills and knowledge in the areas of neuropsychology and neurology with communication interventions. For example, neuroimaging and neuropathological research has demonstrated that individuals with RTT have reduced brain size and cerebral size (Armstrong, 2005; Kaufmann, Pearlson, & Naidu, 1998) cerebral volume (Carter et al., 2008) denderic arborizations (Armstrong, Dunn, Antalffy, & Trivedi, 1995; Armstrong, 2005) and synaptic activity (Moretti, 2006). To date, this research has not connected to clinical intervention planning, for example individuals with RTT typically have impaired dorsal partial grey matter but their occipital cortex is relatively preserved and their anterior frontal lobe reduction correlates to their clinical severity (Carter et al., 2008). The connection between brain imaging and clinical syndromes should directly inform the intervention techniques. Another additional area for clinical psychology research is investigating the impact of communication interventions at the earliest stage of diagnosis, whilst brain development is still maturing. Neuroimaging could investigate the impact of such interventions on denderic arborisation and synaptic activity.

A consistent limitation across both papers is the research generalisability in RTT due to variability in individuals' abilities. A helpful addition to future research would be to include information regarding the Rett Stage. However whilst this might provide an accessible indication of ability this would however Rett Stage would not account for individual ability. A standardised and validated measure of communication and motor ability across all studies would be beneficial.

Moreover, clinical psychologists would have much to offer in the construction and development of appropriate cognitive scales, improving the accuracy of cognitive and communication assessments. This in turn would enable further development of communication ATs.

The scarcity of research across RTT is evident. Both of the papers highlight the challenges in obtaining large sample sizes in RTT research. Researching rare genetic conditions presents particular challenges. For example, in the current climate of psychological research, randomised controlled trials are viewed as the gold standard and case series and case studies are often reported to be of weaker methodological quality (Guo et al., 2016). When researching genetic conditions, researchers will not be able to draw upon such designs that are viewed as holding the most robust experimental designs and sampling methods. As such, case series and case control designs are the only available option for research. This unfortunately means that conditions which are challenging to recruit to are often not featured in research grants and bids. The paucity of research has resulted in a lack of research evidence and translation into clinical practice and health and social policy (Zurynski, Frith, Leonard, & Elliott, 2008). Whilst these papers will assist in providing evidence of behavioural phenotypes and clinical interventions in RTT, the research base needs to evolve. Inter-institutional, inter-disciplinary and international research collaboration is required in order to increase recruitment numbers and disseminate information and clinical expertise (Zurynski et al., 2008)

A key focus of these papers has been the introduction of clinical psychology within the field of RTT and alike genetic syndromes. Within other neurodevelopment conditions such as Autism Spectrum Disorders (ASD) clinical psychologists are often embedded across both

diagnostic services and interventions, often taking a lead in consultancy models for care and management. In addition, psychologists have contributed greatly to research in ASD across areas of assessment, neuroimaging and interventions. This research project has highlighted the valuable contributions psychologists and in particular, clinical psychologists can have in both research and clinical interventions. A strength of these papers is to pave the way in research in these areas.

Dissemination

Dissemination of the systematic review and empirical paper will be via a number of sources. Firstly, the study participants who indicated they would like to receive information regarding the outcome of the study will be sent a summary of the findings. Secondly, Rett UK will be sent a summary and copy of both papers to disseminate via their social media and bimonthly newsletter. Thirdly, a post will be made to social media support organisations of which recruitment was sourced via. Fourthly, both papers have been submitted and are under review with *Journal of Intellectual Disability Res*earch *and Journal of Applied Research in Intellectual Disability* respectively.

Personal and Professional Development

Reflective Process

Upon commencing the Clinical Psychology Doctorate, the author wanted to complete a research project that contributes to clinical practice and develop their confidence in completing research projects. The author hoped to develop experience in conducting research projects alongside clinical work. Prior to this study, the author had commenced a research protocol for another project. The prior project allowed the author to gain experience in developing a research protocol for NHS recruitment and the NHS ethics procedures. Although this project was not viable for the Doctorate in Clinical Psychology requirements, the author learnt a lot about the processes and challenges in commencing a research project for the NHS.

The author did have some reservations about their inexperience of working clinically with RTT and completing research into a medically and genetically dominated domain. In addition the author had uncertainties about the level of medical expertise needed when researching RTT. However, from working within intellectual disability services previously, the author felt confident in being able to overcome these challenges by taking a practical approach of self-directed learning. Their previous experience further provided them with enthusiasm and passion to conduct research into rare genetic conditions which are often over-looked when

it comes to the involvement of clinical psychology in favour of those relatively more common neurodevelopmental disorders.

While the author initially found some of the terminology and concepts of genetic research difficult to grasp, collaborating with a Clinical Geneticist has aided the authors understanding of the terminology and concepts of individuals living with RTT. This collaboration has been particularly helpful in the developing the language in the research paper to be more accessible and relatable for families. In addition, the links that were established with Rett UK and the social media support groups assisted the author in their knowledge of the everyday challenges that individuals with RTT and their carers face. Whilst these individuals may well be more likely to seek such support when they are in crisis, it allowed the author to reflect on carer's ability to engage in research projects when their children's difficulties were so profound and at times were experiencing severe medical challenges.

Conducting the research as a whole has assisted the author in their development and confidence in their ability to conduct research. The author has enjoyed the process and hopes to continue to conduct research alongside a clinical role to assist in the contributions to evidence-based practice.

Competency Development

This culmination of this thesis development has assisted in the development of the author's personal, professional and research skills.

Transferable skills

As discussed, psychological involvement in rare genetic disorders are largely absent. This project allowed the author to draw upon their transferrable skills and apply it to an area of which their knowledge was modest. Whilst this was initially daunting, the process allowed the author to develop confidence in working within unfamiliar areas. As such, it highlighted the adaptable skills that a Clinical Psychologist can bring to both research and clinical applications of research that could otherwise be overlooked.

Assessment

The use of the ABQ allowed for attenuated behaviours to be assessed in a standardised manner. The use of standardised measures is imperative in research. However, the author reflected that within clinical settings, a standardised measure would not be used in isolation; with the clinician drawing upon clinical experience.

Personal and professional

This project allowed the author to work with a high level of autonomy. Supervision was used to refine research ideas. The project has allowed the author to develop their academic writing skills towards a journal article format. In particular their adaptation to writing in a more succinct manner and identifying the most relevant points and literature to include. This was particularly relevant given there was a low word count for both of the journal's the articles were prepared for. The skills learnt will assist the author in their confidence and ability to conduct research post qualification.

Service user and carer involvement

Upon reflection, an area which could have been improved in the research project is service user and carer involvement. The project would be challenging to include service user involvement; however carer involvement would have assisted in improving the research process by providing a different outlook on the project (Research Design Service London). In line with the National Institute for Health Research (2014) involvement could have been introduced in the initial development of the research ideas, research design and assisted in the dissemination of the research findings. As this was a doctoral thesis, the author would have had to undertake the data collection and analysis. In addition the research would not have been able to be 'user led or controlled'. However, carers could have inputted to the project in a consultative and collaborative capacity. A particular benefit to this project would have been service user and carer involvement in additional assistance of identifying possible recruitment avenues and reviewing of the information sheets and consent forms with the view to improve recruitment or highlight barriers to recruitment.

The author's engagement with social media support groups during the recruitment phase raised some moral dilemmas for the author. Individuals within the social media support forum had created very strong 'RTT community' bonds and provided a great deal of emotional support to each other. At times there was a wariness of both researchers and clinicians. Conducting research in such groups allowed the author to reflect on if entering their forum for research purposes was in some way unintentionally voyeuristic and intrusive. The researcher did approach each admin prior to this, however, on reflection, they queried if they should have asked the admin to provide the information as opposed to 'joining' the group. When thinking about future research development projects the author will approach future projects differently.

Leadership

Throughout the development of this thesis, a number of leadership skills were both developed and utilised. The author's primary objection was to build successful relationships with experts in the field of RTT in order to assist in the development and support of the research project. Being relatively new to learning about RTT and working with such experienced and knowledgeable clinicians could be a daunting process. However, by taking a lead of the project allowed the author to showcase the skills and expertise that Clinical Psychologist can bring. By being transparent about their gaps in knowledge of genetics and medical interventions and focusing on their own skills, allowed the author to take lead on the project which was an exciting opportunity.

Such skills will assist in the author's future development as a clinical psychologist and as a researcher. Clinical Psychologists are required to establish working relationships with others in order to achieve fruition of tasks (BPS, 2010). As discussed, to date, research into RTT has been under represented by Clinical Psychology and thus, this provided an opportunity to highlight the value and skill set of Clinical Psychology working within this population both clinically and via research. This has led to the planning of future research collaborations between the Welsh Genetics Centre and the Doctorate in Clinical Psychology Training Programme.

References

Ahonniska-Assa, J., Polack, O., Saraf, E., Wine, J., Silberg, T., Nissenkorn, A., & Ben-Zeev, B. (2018). Assessing cognitive functioning in females with Rett syndrome by eye-tracking methodology. *European Journal of Paediatric Neurology*, *22*(1), 39–45. http://doi.org/10.1016/j.ejpn.2017.09.010

Armstrong, D., Dunn, J. K., Antalffy, B., & Trivedi, R. (1995). Selective dendritic alterations in the cortex of rett syndrome. *Journal of Neuropathology and Experimental Neurology*, *54*(2), 195–201. http://doi.org/10.1097/00005072-199503000-00006

Auger, C., Hernando, V., & Galmiche, H. (2017). Use of Mechanical Insufflation-Exsufflation Devices for Airway Clearance in Subjects With Neuromuscular Disease. *Respiratory Care*, *62*(2), 236–245. http://doi.org/10.4187/respcare.04877

Bell, L., Oliver, C., Wittkowski, A., Moss, J., & Hare, D. (2018). Attenuated behaviour in Cornelia de Lange and fragile X syndromes. *Journal of Intellectual Disability Research*. http://doi.org/10.1111/jir.12481

Boland, A., Cherry, M. G., & Dickson, R. (2014). *Doing a systematic review: a student's guide*. *Igarss 2014*. http://doi.org/10.1007/s13398-014-0173-7.2

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

BPS. (2010). *The Clinical Psychology Leadership Development Framework*. Leicester.

Breen, J., & Hare, D. J. (2017). The nature and prevalence of catatonic symptoms in young people with autism. *Journal of Intellectual Disability Research*, *61*(6), 580–593. http://doi.org/10.1111/jir.12362

Cardoza, B., Clarke, A., Wilcox, J., Gibbon, F., Smith, P. E. M., Archer, H., … Kerr, M. (2011). Epilepsy in Rett syndrome: association between phenotype and genotype, and implications for practice. *Seizure : The Journal of the British Epilepsy Association*, *20*(8), 646–9. http://doi.org/10.1016/j.seizure.2011.06.010

Carter, J. C., Lanham, D. C., Pham, D., Bibat, G., Naidu, S., & Kaufmann, W. E. (2008). Selective cerebral volume reduction in Rett syndrome: a multiple-approach MR imaging study. *AJNR American Journal of Neuroradiology*, *29*(3), 436–441. http://doi.org/10.3174/ajnr.A0857

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

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

Cianfaglione, R., Clarke, A., Kerr, M., Hastings, R. P., Oliver, C., Moss, J., … Felce, D. (2015). A national survey of Rett syndrome: behavioural characteristics. *Journal of Neurodevelopmental Disorders*, *7*, 11. http://doi.org/10.1186/s11689-015-9104-y

Cianfaglione, R., Hastings, R. P., Felce, D., Clarke, A., & Kerr, M. P. (2015). Psychological

Well-Being of Mothers and Siblings in Families of Girls and Women with Rett Syndrome. *Journal of Autism and Developmental Disorders*, *45*(9), 2939–2946. http://doi.org/10.1007/s10803-015-2457-y

Cianfaglione, R., Hastings, R. P., Felce, D., Clarke, A., & Kerr, M. P. (2017). Change over a 16-month period in the psychological well-being of mothers of girls and women with Rett syndrome. *Developmental Neurorehabilitation*, *20*(5), 261–265. http://doi.org/10.3109/17518423.2016.1142483

Cowley, D. E. (1995). Prostheses for primary total hip replacement. A critical appraisal of the literature. *International Journal of Technology Assessment in Health Care*, *11*(4), 770–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8567209

DeJong, H., Bunton, P., & Hare, D. J. (2014). A systematic review of interventions used to treat catatonic symptoms in people with autistic spectrum disorders. *Journal of Autism and Developmental Disorders*, *44*(9), 2127–2136. http://doi.org/10.1007/s10803-014-2085-y

Djukic, A., Valicenti McDermott, M., Mavrommatis, K., & Martins, C. L. (2012). Rett Syndrome: Basic Features of Visual Processing—A Pilot Study of Eye-Tracking. *Pediatric Neurology*, *47*(1), 25–29. http://doi.org/10.1016/j.pediatrneurol.2012.04.009

Duncan Armstrong, D. (2005). Neuropathology of Rett Syndrome. *Journal of Child Neurology*, *20*(9), 747–753. http://doi.org/10.1177/08830738050200090901

Dykens, E. M. (1995). Measuring behavioral phenotypes: Provocations from the“ new genetics.” *American Journal on Mental Retardation*, *99*(5), 522–532. Retrieved from http://psycnet.apa.org/psycinfo/1995-29741-001

Efron, B., & Tibshirani, R. (1994). *An introduction to the bootstrap*. Chapman & Hall. Retrieved

from https://www.crcpress.com/An-Introduction-to-the-Bootstrap/Efron-Tibshirani/p/book/9780412042317

Felce, D., & Perry, J. (1995). Quality of life: Its definition and measurement. *Research in Developmental Disabilities*, *16*(1), 51–74. http://doi.org/10.1016/0891-4222(94)00028-8

Field, A. (2013). Discovering Statistics using IBM SPSS Statistics. *Discovering Statistics Using IBM SPSS Statistics*, 297–321. http://doi.org/10.1016/B978-012691360-6/50012-4

Flint, J. (1996). Behaviour phenotypes: A window on to the biology of behavior. *Journal of Child Psychology and Psychiatry*, *37*(4), 355–367. http://doi.org/10.1111/j.1469 7610.1996.tb01417.x

Garg, A. X., Hackam, D., & Tonelli, M. (2008). Systematic review and meta-analysis: When one study is just not enough. *Clinical Journal of the American Society of Nephrology*. http://doi.org/10.2215/CJN.01430307

Glaze, D. G., Schultz, R. J., & Frost, J. D. (1998). Rett syndrome: Characterization of seizures versus non-seizures. *Electroencephalography and Clinical Neurophysiology*, *106*, 79–83. http://doi.org/10.1016/S0013-4694(97)00084-9

Guo, B., Moga, C., Harstall, C., & Schopflocher, D. (2016). A principal component analysis is conducted for a case series quality appraisal checklist. *Journal of Clinical Epidemiology*, *69*, 199–207.e2. http://doi.org/10.1016/j.jclinepi.2015.07.010

Gutowski, S. J. (1996). Response acquisition for music or beverages in adults with profound multiple handicaps. *Journal of Developmental and Physical Disabilities*, *8*(3), 221–231. http://doi.org/10.1007/BF02578391

Hare, D. J., & Malone, C. (2004). Catatonia and autistic spectrum disorders. *Autism : The*

International Journal of Research and Practice, *8*(2), 183–195. http://doi.org/10.1177/1362361304042722

Higgins, J. P. T., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., … Sterne, J. A. C. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*, *343*(oct18 2), d5928–d5928. http://doi.org/10.1136/bmj.d5928

Ivancic, M. T., & Bailey, J. S. (1996). Current limits to reinforcer identification for some persons with profound multiple disabilities. *Research in Developmental Disabilities*, *17*(1), 77–92. http://doi.org/10.1016/0891-4222(95)00038-0

Jesson, J., Matheson, L., & Lacey, F. M. (2011). The Systematic Review. In *Doing your literature review: Traditional and systematic techniques* (pp. 103–130).

Kaufmann, W. E., Pearlson, G. D., & Naidu, S. (1998). The neuroanatomy of Rett syndrome: neuropathological and neuroimaging studies. *Rivista Medica*, *4*(4), 187–199.

Lancioni, G. E., O'reilly, M. F., Singh, N. N., Sigafoos, J., Oliva, D., & Severini, L. (2008). Three persons with multiple disabilities accessing environmental stimuli and asking for social contact through microswitch and VOCA technology. *Journal of Intellectual Disability Research*, *52*(4), 327–336. http://doi.org/10.1111/j.1365-2788.2007.01024.x

Lancioni, G. E., O'Reilly, M. F., Singh, N. N., Sigafoos, J., Oliva, D., & Severini, L. (2008). Enabling two persons with multiple disabilities to access environmental stimuli and ask for social contact through microswitches and a VOCA. *Research in Developmental Disabilities*, *29*(1), 21–28. http://doi.org/10.1016/j.ridd.2006.10.001

Moga, C., Guo, B., Schopflocher, D., & Harstall, C. (2012). *Development of a quality appraisal tool for case series studies using a modified Delphi technique*.

Moher D, A, L., & Tetzlaff J. (2009). Preferred Reporting Items for Systematic Reviews and Meta Analyses: The PRISMA Statement. *PLOS Medicine*. http://doi.org/10.1371/journal.pmed1000097

Moretti, P. (2006). Learning and Memory and Synaptic Plasticity Are Impaired in a Mouse Model of Rett Syndrome. *Journal of Neuroscience*, *26*(1), 319–327. http://doi.org/10.1523/JNEUROSCI.2623-05.2006

Neul, J. L., Kaufmann, W. E., Glaze, D. G., Christodoulou, J., Clarke, A. J., Bahi-Buisson, N., … Percy, A. K. (2010). Rett syndrome: Revised diagnostic criteria and nomenclature. *Annals of Neurology*, *68*(6), 944–950. http://doi.org/10.1002/ana.22124

Parisi, L., Filippo, T. Di, & Roccella, M. (2016). The quality of life in girls with Rett syndrome. *Mental Illness*, *8*(1). http://doi.org/10.4081/mi.2016.6302

Patterson, J. F. (1986). Akinetic parkinsonism and the catatonic syndrome: An overview. *Southern Medical Journal*, *79*(6), 682–685. http://doi.org/10.1097/00007611-198606000-00008

Perelmutter, B., McGregor, K. K., & Gordon, K. R. (2017). Assistive technology interventions for adolescents and adults with learning disabilities: An evidence-based systematic review and meta-analysis. *Computers & Education*, *114*, 139–163. http://doi.org/10.1016/j.compedu.2017.06.005

Roland, L. T., Skillington, S. A., & Ogden, M. A. (2017). Sialendoscopy-assisted transfacial removal of parotid sialoliths: A systematic review and meta-analysis. *The Laryngoscope*, *127*(11), 2510–2516. http://doi.org/10.1002/lary.26610

Rose, S. A., Djukic, A., Jankowski, J. J., Feldman, J. F., Fishman, I., & Valicenti-Mcdermott, M. (2013). Rett syndrome: An eye-tracking study of attention and recognition memory.

Developmental Medicine and Child Neurology, *55*(4), 364–371. http://doi.org/10.1111/dmcn.12085

Sigafoos, J., Green, V. A., Schlosser, R., O'eilly, M. F., Lancioni, G. E., Rispoli, M., & Lang, R. (2009). Communication intervention in Rett syndrome: A systematic review. *Research in Autism Spectrum Disorders*. http://doi.org/10.1016/j.rasd.2008.09.006

Sigafoos, J., Kagohara, D., Van Der Meer, L., Green, V. A., O'Reilly, M. F., Lancioni, G. E., … Zisimopoulos, D. (2011). Communication assessment for individuals with Rett syndrome: A systematic review. *Research in Autism Spectrum Disorders*, *5*(2), 692–700. http://doi.org/10.1016/j.rasd.2010.10.006

Simacek, J., Reichle, J., & McComas, J. J. (2016). Communication Intervention to Teach Requesting Through Aided AAC for Two Learners With Rett Syndrome. *Journal of Developmental and Physical Disabilities*, *28*(1), 59–81. http://doi.org/10.1007/s10882-015-9423-7

Tarquinio, D. C., & Percy, A. K. (2016). Rett Syndrome. In *Neuronal and Synaptic Dysfunction in Autism Spectrum Disorder and Intellectual Disability* (pp. 301–323). Elsevier. http://doi.org/10.1016/B978-0-12-800109-7.00019-4

Vere, J., & Joshi, R. (2012). Quality assessment of prospective case series of dental implant surgery and prosthodontics published between 2004 and 2008: a systematic review. *The International Journal of Oral & Maxillofacial Implants*, *27*(4), 865–874.

Waite, J., Heald, M., Wilde, L., Woodcock, K., Welham, A., Adams, D., & Oliver, C. (2014). The importance of understanding the behavioural phenotypes of genetic syndromes associated with intellectual disability. *Paediatrics and Child Health (United Kingdom)*. http://doi.org/10.1016/j.paed.2014.05.002

Weaving, L. S., Ellaway, C. J., Gécz, J., & Christodoulou, J. (2005). Rett syndrome: clinical review and genetic update. *Journal of Medical Genetics*, *42*(1), 1–7. http://doi.org/10.1136/jmg.2004.027730

Williams, J., & MacKinnon, D. P. (2008). Resampling and distribution of the product methods for testing indirect effects in complex models. *Structural Equation Modeling*, *15*(1), 23–51. http://doi.org/10.1080/10705510701758166

Wing, L., & Shah, A. (2000). Catatonia in autistic spectrum disorders. *The British Journal of Psychiatry : The Journal of Mental Science*, *176*, 357–362. http://doi.org/10.1192/bjp.176.4.357

Yang, A. W., Li, C. G., Da Costa, C., Allan, G., Reece, J., & Xue, C. C. (2009). Assessing quality of case series studies: development and validation of an instrument by herbal medicine CAM researchers. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, *15*(5), 513–522. http://doi.org/10.1089/acm.2007.0806

Young, J., Fry-Smith, A., & Hyde, C. (1999). Lung volume reduction surgery (LVRS) for chronic obstructive pulmonary disease (COPD) with underlying severe emphysema. *Thorax*, *54*(9), 779–89. http://doi.org/10.1136/thx.54.9.779

Zeng, X., Zhang, Y., Kwong, J. S. W., Zhang, C., Li, S., Sun, F., … Du, L. (2015). The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. *Journal of Evidence-Based Medicine*, *8*(1), 2–10. http://doi.org/10.1111/jebm.12141

Zurynski, Y., Frith, K., Leonard, H., & Elliott, E. (2008). Rare childhood diseases: How should we respond? *Archives of Disease in Childhood*. http://doi.org/10.1136/adc.2007.134940

Appendices

Appendix 1: Author guidelines for Journal of Applied Research in Intellectual Disabilities

Crosscheck

The journal to which you are submitting your manuscript employs a plagiarism detection system. By submitting your manuscript to this journal you accept that your manuscript may be screened for plagiarism against previously published works.

1. GENERAL

The *Journal of Applied Research in Intellectual Disabilities* is an international, peer-reviewed journal which draws together findings derived from original applied research in intellectual disabilities. The journal is an important forum for the dissemination of ideas to promote valued lifestyles for people with intellectual disabilities. It reports on research from the UK and overseas by authors from all relevant professional disciplines. It is aimed at an international, multi-disciplinary readership.

The topics it covers include community living, quality of life, challenging behaviour, communication, sexuality, medication, ageing, supported employment, family issues, mental health, physical health, autism, economic issues, social networks, staff stress, staff training, epidemiology and service provision. Theoretical papers are also considered provided the implications for therapeutic action or enhancing quality of life are clear. Both quantitative and qualitative methodologies are welcomed. All original and review articles continue to undergo a rigorous, peer-refereeing process.

Please read the instructions below carefully for details on submission of manuscripts, the journal's requirements and standards as well as information concerning the procedure after a manuscript has been accepted for publication. Authors are encouraged to visit http://authorservices.wiley.com/bauthor/ for further information on the preparation and submission of articles.

All manuscripts must be submitted solely to this journal and not published, in press, or submitted elsewhere.

2. ETHICAL GUIDELINES

Acceptance of papers is based on the understanding that authors have treated research participants with respect and dignity throughout. Please see Section 2.2 below.

2.1 Authorship and Acknowledgements

Authorship: Authors submitting a paper do so on the understanding that the manuscript has been read and approved by all authors and that all authors agree to the submission of the manuscript to the journal. ALL named authors must have made an active contribution to the conception and design and/or analysis and interpretation of the data and/or the drafting of the paper and ALL authors must have critically reviewed its content and have approved the final version submitted for publication. Participation solely in the acquisition of funding or the collection of data does not justify authorship.

It is a requirement that all authors have been accredited as appropriate under submission of the manuscript. Contributors who do not qualify as authors should be mentioned under Acknowledgements.

Acknowledgements: Under Acknowledgements please specify contributors to the article other than the authors accredited. Please also include specifications of the source of funding for the study and any potential conflict of interest if appropriate. Suppliers of materials should be named and their location (town, state/county, country) included.

2.2 Ethical Approvals

Research involving human participants will only be published if such research has been conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version, 2002 www.wma.net) and the additional requirements, if any, of the country where the research has been carried out. Manuscripts must be accompanied by a statement that the research was undertaken with the understanding and written consent of each participant (or the participant's representative, if they lack capacity), and according to the above mentioned principles. A statement regarding the fact that the study has been independently reviewed and approved by an ethical board should also be included.

All studies using human participants should include an explicit statement in the Material and Methods section identifying the review and ethics committee approval for each study, if applicable. Editors reserve the right to reject papers if there is doubt as to whether appropriate procedures have been used.

Ethics of investigation: Papers not in agreement with the guidelines of the Helsinki Declaration as revised in 1975 will not be accepted for publication.

2.3 Clinical Trials

Clinical trials should be reported using the CONSORT guidelines available at www.consort-statement.org. A CONSORT checklist should also be included in the submission material (www.consort-statement.org).

The *Journal of Applied Research in Intellectual Disabilities* encourages authors submitting manuscripts reporting from a clinical trial to register the trials in any of the following free, public trials registries: www.clinicaltrials.org, www.isrctn.org. The clinical trial registration number and name of the trial register will then be published with the paper.

2.4 Conflict of Interest and Source of Funding

Conflict of Interest: Authors are required to disclose any possible conflict of interest. These include financial (for example patent ownership, stock ownership, consultancies, speaker's fee). Author's conflict of interest (or information specifying the absence of conflict of interest) will be published under a separate heading.

The *Journal of Applied Research in Intellectual Disabilities* requires that sources of institutional, private and corporate financial support for the work within the manuscript must be fully acknowledged, and any potential conflict of interest noted. As of 1st March 2007, this information is a requirement for all manuscripts submitted to the journal and will be published in a highlighted box on the title page of the article. Please include this information under the separate headings of 'Source of Funding' and 'Conflict of Interest' at the end of the manuscript.

If the author does not include a conflict of interest statement in the manuscript, then the following statement will be included by default: 'No conflict of interest has been declared'.

Source of Funding: Authors are required to specify the source of funding for their research when submitting a paper. Suppliers of materials should be named and their location (town, state/county, country) included. The information will be disclosed in the published article.

2.5 Permissions

If all or parts of previously published illustrations are used, permission must be obtained from the copyright holder concerned. It is the author's responsibility to obtain these in writing and provide copies to the Publishers.

2.6 Copyright Assignment

If your paper is accepted, the author identified as the formal corresponding author for the paper will receive an email prompting them to login into Author Services; where via the Wiley Author Licensing Service (WALS) they will be able to complete the license agreement on behalf of all authors on the paper.

<u>For authors signing the copyright transfer agreement</u>

If the OnlineOpen option is not selected the corresponding author will be presented with the copyright transfer agreement (CTA) to sign. The terms and conditions of the CTA can be previewed in the samples associated with the Copyright FAQs below:

CTA Terms and Conditions http://authorservices.wiley.com/bauthor/faqs_copyright.asp

3. ONLINEOPEN

<u>For authors choosing OnlineOpen</u>

If the OnlineOpen option is selected the corresponding author will have a choice of the following Creative Commons License Open Access Agreements (OAA):

Creative Commons Attribution License OAA

Creative Commons Attribution Non-Commercial License OAA

Creative Commons Attribution Non-Commercial -NoDerivs License OAA

To preview the terms and conditions of these open access agreements please visit the Copyright FAQs hosted on Wiley Author Services http://authorservices.wiley.com/bauthor/faqs_copyright.aspand
visit http://www.wileyopenaccess.com/details/content/12f25db4c87/Copyright--License.html.
If you select the OnlineOpen option and your research is funded by The Wellcome Trust and members of the Research Councils UK (RCUK) you will be given the opportunity to publish your article under a CC-BY license supporting you in complying with Wellcome Trust and Research Councils UK requirements. For more information on this policy and the Journal's compliant self-archiving policy please visit: http://www.wiley.com/go/funderstatement.

4. SUBMISSION OF MANUSCRIPTS

Submissions are now made online using ScholarOne Manuscripts (formerly Manuscript Central). To submit to the journal go to http:// mc.manuscriptcentral.com/jarid. If this is the first time you have used the system you will be asked to register by clicking on 'create an account'. Full instructions on making your submission are provided. You should receive an acknowledgement within a few minutes. Thereafter, the system will keep you informed of the process of your submission through refereeing, any revisions that are required and a final decision.

4.1 Manuscript Files Accepted

Manuscripts should be uploaded as Word (.doc) or Rich Text Format (.rft) files (not write-protected) plus separate figure files. GIF, JPEG, PICT or Bitmap files are acceptable for submission, but only high-resolution TIF or EPS files are suitable for printing.

To allow double-blinded review, please upload your manuscript and title page as **separate** files.

Please upload:
1. Your manuscript without title page under the file designation 'main document'.
2. Figure files under the file designation 'figures'.
3. Title page which should include title, authors (including corresponding author contact details), acknowledgements and conflict of interest statement where applicable, should be uploaded under the file designation 'title page'.

All documents uploaded under the file designation 'title page' will not be viewable in the HTML and PDF format you are asked to review at the end of the submission process. The files viewable in the HTML and PDF format are the files available to the reviewer in the review process.
Please note that any manuscripts uploaded as Word 2007 (.docx) will be automatically rejected. Please save any .docx files as .doc before uploading.

4.2 Blinded Review

All articles submitted to the journal are assessed by at least two anonymous reviewers with expertise in that field. The Editors reserve the right to edit any contribution to ensure that it conforms with the requirements of the journal.

5. MANUSCRIPT TYPES ACCEPTED

Original Articles, Review Articles, Brief Reports, Book Reviews and ***Letters to the Editor*** are accepted. ***Theoretical Papers*** are also considered provided the implications for therapeutic action or enhancing quality of life are clear. Both quantitative and qualitative methodologies are welcomed. Articles are accepted for publication only at the discretion of the Editor. Articles should not exceed 7000 words. Brief Reports should not normally exceed 2000 words. Submissions for the Letters to the Editor section should be no more than 750 words in length.

6. MANUSCRIPT FORMAT AND STRUCTURE

6.1 Format

Language: The language of publication is English. Authors for whom English is a second language must have their manuscript professionally edited by an English speaking person before submission to make sure the English is of high quality. It is preferred that manuscripts are professionally edited. A list of independent suppliers of editing services can be found at http://authorservices.wiley.com/bauthor/english_language.asp. All services are paid for and arranged by the author, and use of one of these services does not guarantee acceptance or preference for publication.

6.2 Structure

All manuscripts submitted to the *Journal of Applied Research in Intellectual Disabilities* should include:

Cover Page: A cover page should contain only the title, thereby facilitating anonymous reviewing. The authors' details should be supplied on a separate page and the author for correspondence should be identified clearly, along with full contact details, including e-mail address.

Running Title: A short title of not more than fifty characters, including spaces, should be provided.

Keywords: Up to six key words to aid indexing should also be provided.

Main Text: All papers should have a structured abstract (maximum 150 words) as follows: Background, Method, Results, and Conclusions. The abstract should provide an outline of the research questions, the design, essential findings and main conclusions of the study. Authors should make use of headings within the main paper as follows: Introduction, Method, Results and Discussion. Subheadings can be used as appropriate. All authors must clearly state their research questions, aims or hypotheses clearly at the end of the Introduction. Figures and Tables should be submitted as a separate file.

Style: Manuscripts should be formatted with a wide margin and double spaced. Include all parts of the text of the paper in a single file, but do not embed figures. Please note the following points which will help us to process your manuscript successfully:

-Include all figure legends, and tables with their legends if available.

-Do not use the carriage return (enter) at the end of lines within a paragraph.

-Turn the hyphenation option off.

-In the cover email, specify any special characters used to represent non-keyboard characters.

-Take care not to use l (ell) for 1 (one), O (capital o) for 0 (zero) or ß (German esszett) for (beta).

-Use a tab, not spaces, to separate data points in tables.

-If you use a table editor function, ensure that each data point is contained within a unique cell, i.e. do not use carriage returns within cells.

Spelling should conform to *The Concise Oxford Dictionary of Current English* and units of measurements, symbols and abbreviations with those in *Units, Symbols and Abbreviations* (1977) published and supplied by the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. This specifies the use of S.I. units.

6.3 References

APA - American Psychological Association

References should be prepared according to the Publication Manual of the American Psychological Association (6th edition). This means in text citations should follow the author-date method whereby the author's last name and the year of

publication for the source should appear in the text, for example, (Jones, 1998). The complete reference list should appear alphabetically by name at the end of the paper.

A sample of the most common entries in reference lists appears below. Please note that a DOI should be provided for all references where available. For more information about APA referencing style, please refer to the APA FAQ. Please note that for journal articles, issue numbers are not included unless each issue in the volume begins with page one.

Journal article

Example of reference with 2 to 7 authors

Beers, S. R. , & De Bellis, M. D. (2002). Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. The American Journal of Psychiatry, 159, 483–486. doi:10.1176/appi.ajp.159.3.483

Ramus, F., Rosen, S., Dakin, S. C., Day, B. L., Castellote, J. M., White, S., & Frith, U. (2003). Theories of developmental dyslexia: Insights from a multiple case study of dyslexic adults. *Brain, 126*(4), 841-865. doi: 10.1093/brain/awg076

Example of reference with more than 7 authors

Rutter, M., Caspi, A., Fergusson, D., Horwood, L. J., Goodman, R., Maughan, B., ... Carroll, J. (2004). Sec differences in developmental reading disability: New findings from 4 epidomiological studies. *Journal of the American Medical Association, 291*(16), 2007-2012. doi 10.1001/jama.291.16.2007

Book Edition

Bradley-Johnson, S. (1994). Psychoeducational assessment of students who are visually impaired or blind: Infancy through high school (2nd ed.). Austin, TX: Pro-ed.

6.4 Tables, Figures and Figure Legends

Tables should include only essential data. Each table must be typewritten on a separate sheet and should be numbered consecutively with Arabic numerals, e.g. Table 1, and given a short caption.

Figures should be referred to in the text as Figures using Arabic numbers, e.g. Fig.1, Fig.2 etc, in order of appearance. Figures should be clearly labelled with the name of the first author, and the appropriate number. Each figure should have a separate legend; these should be grouped on a separate page at the end of the manuscript. All symbols and abbreviations should be clearly explained. In the full-text online edition of the journal, figure legends may be truncated in abbreviated links to the full screen version. Therefore, the first 100 characters of any legend should inform the reader of key aspects of the figure.

Preparation of Electronic Figures for Publication

Although low quality images are adequate for review purposes, print publication requires high quality images to prevent the final product being blurred or fuzzy. Submit EPS (line art) or TIFF (halftone/photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Do not use pixel-oriented programmes. Scans (TIFF only) should have a resolution of at least 300 dpi (halftone) or 600 to 1200 dpi (line drawings) in relation to the reproduction size. Please submit the data for figures in black and white or submit a Colour Work Agreement Form. EPS files should be saved with fonts embedded (and with a TIFF preview if possible).

Further information can be obtained at Wiley-Blackwell's guidelines for figures: http://authorservices.wiley.com/bauthor/illustration.asp.

Check your electronic artwork before submitting it: http://authorservices.wiley.com/bauthor/eachecklist.asp.

Permissions: If all or parts of previously published illustrations are used, permission must be obtained from the copyright holder concerned. It is the author's responsibility to obtain these in writing and provide copies to the Publisher.

Colour Charges: It is the policy of the *Journal of Applied Research in Intellectual Disabilities* for authors to pay the full cost for the reproduction of their colour artwork. Colour Work Agreement Form can be downloaded here.

7. AFTER ACCEPTANCE

Upon acceptance of a paper for publication, the manuscript will be forwarded to the Production Editor who is responsible for the production of the journal.

7.1 Proof Corrections

The corresponding author will receive an e-mail alert containing a link to a website. A working e-mail address must therefore be provided for the corresponding author. The proof can be downloaded as a PDF file from this site.

Acrobat Reader will be required in order to read this file. This software can be downloaded (free of charge) from the following website:
www.adobe.com/products/acrobat/readstep2.html
This will enable the file to be opened, read on screen, and printed out in order for any corrections to be added. Further instructions will be sent with the proof. Proofs will be posted if no e-mail address is available; in your absence, please arrange for a colleague to access your e-mail to retrieve the proofs.

Proofs must be returned to the Production Editor within 3 days of receipt.
As changes to proofs are costly, we ask that you only correct typesetting errors. Excessive changes made by the author in the proofs, excluding typesetting errors, will be charged separately. Other than in exceptional circumstances, all illustrations are retained by the Publisher. Please note that the author is responsible for all statements made in their work, including changes made by the copy editor.

7.2 Early View (Publication Prior to Print)

The *Journal of Applied Research in Intellectual Disabilities* is covered by Wiley-Blackwell's Early View service. Early View articles are complete full-text articles published online in advance of their publication in a printed issue. Early View articles are complete and final. They have been fully reviewed, revised and edited for publication, and the authors' final corrections have been incorporated. Because they are in final form, no changes can be made after online publication. The nature of Early View articles means that they do not yet have a volume, issue or page number, so Early View articles cannot be cited in the traditional way. They are therefore given a DOI (digital object identifier) which allows the article to be cited and tracked before it is allocated to an issue. After print publication, the DOI remains valid and can continue to be used to cite and access the article.

7.3 Author Services

Online production tracking is available for your article through Wiley-Blackwell's Author Services. Author Services enables authors to track their article - once it has been accepted - through the production process to publication online and in print. Authors can check the status of their articles online and choose to receive automated e-mails at key stages of production. The author will receive an e-mail with a unique link that enables them to register and have their article automatically added to the system. Please ensure that a complete e-mail address is provided when submitting the manuscript. Visit http://authorservices.wiley.com/bauthor/ for more details on online production tracking and for a wealth of resources include FAQs and tips on article preparation, submission and more.
For more substantial information on the services provided for authors, please see Wiley-Blackwell's Author Services.

7.4 Author Material Archive Policy

Please note that unless specifically requested, Wiley-Blackwell will dispose of all hardcopy or electronic material submitted two issues after publication. If you require the return of any material submitted, please inform the editorial office or Production Editor as soon as possible.

7.5 Offprints and Extra Copies

Free access to the final PDF offprint of the article will be available via Author Services only. Additional paper offprints may be ordered online. Please click on the following link, fill in the necessary details and ensure that you type information in all of the required fields: http://offprint.cosprinters.com/blackwell

If you have queries about offprints please email offprint@cosprinters.com

Appendix 2: Author guidelines for Journal of Intellectual Disabilities Research

Content of Author Guidelines:

1. Editorial and Content Considerations
2. Ethical Guidelines
3. Manuscript Types Accepted
4. Preparation of Your Manuscript
5. Submitting Your Manuscript
6. Copyright, Licencing and Online Open
7. Post Acceptance
8. Post Publication

Quick links: JIDR Submission Site, Wiley's Resources for Journal Authors

Relevant Documents Colour Work Agreement Form

1. EDITORIAL AND CONTENT CONSIDERATIONS

Journal of Intellectual Disability Research is devoted exclusively to the scientific study of intellectual disability and publishes papers reporting original observations in this field. The subject matter is broad and includes, but is not restricted to, findings from biological, educational, genetic, medical, psychiatric, psychological and sociological studies, and ethical, philosophical, and legal contributions that increase knowledge on the treatment and prevention of intellectual disability and of associated impairments and disabilities, and/or inform public policy and practice.

The journal publishes Full Reports, Brief Reports and Systematic Reviews. Mental Health Special Editions are published quarterly. Narrative reviews and hypothesis papers are encouraged but authors should discuss the focus of their review with the Editor in Chief prior to submission to ensure it is appropriate for the journal. Submissions for Book Reviews are also welcomed. Case studies are **not** published by JIDR.

Journal of Intellectual Disability Research will feature four Annotation articles each year covering a variety of topics of relevance to the main aims of the journal or topics. Senior researchers, academics and clinicians of recognised standing in their field will be invited to write an Annotation for the journal covering an area that will be negotiated with the Editor in Chief, Prof. Chris Oliver, on behalf of the Editorial Team.

Peer Review Process

The acceptance criteria for all papers are the quality and originality of the research and its significance to our readership. Except where otherwise stated, manuscripts are double-blind peer reviewed by two anonymous reviewers and the editor.

Journal of Intellectual Disability Research attempts to keep the review process as short as possible to enable rapid publication of new scientific data. In order to facilitate this process, submitting authors are asked to suggest the names and current e-mail addresses of two potential reviewers whom you consider capable of reviewing your manuscript. In addition to your choice the journal editor will choose one or two reviewers as well. Suggestions will be requested via the submission system.

Authors who wish to appeal the decision on their submitted paper may do so by e-mailing the Editorial Office with a detailed explanation for why they find reasons to appeal the decision.

Plagiarism detection

• The journal employs a plagiarism detection system. By submitting your manuscript to this journal you accept that your manuscript may be screened for plagiarism against previously published works.

• Individual authors and researchers can now check their work for plagiarism before submission - please click here for details.

2. ETHICAL GUIDELINES

Journal of Intellectual Disability Research adheres to the ethical guidelines for publication and research summarised below.

Authorship and Acknowledgements

Authorship: Authors submitting a paper do so on the understanding that the manuscript has been read and approved by all authors and that all authors agree to the submission of the manuscript to the journal. ALL named authors must have made an active contribution to the conception and design and/or analysis and interpretation of the data and/or the drafting of the paper and ALL must have critically reviewed its content and have approved the final version submitted for publication. Participation solely in the acquisition of funding or the collection of data does not justify authorship and, except in the case of complex large-scale or multi-centre research.

Journal of Intellectual Disability Research adheres to the definition of authorship set up by The International Committee of Medical Journal Editors (ICMJE). According to the ICMJE authorship criteria should be based on 1) substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content and 3) final approval of the version to be published. Authors should meet conditions 1, 2 and 3.

It is a requirement that all authors have been accredited as appropriate upon submission of the manuscript. Contributors who do not qualify as authors should be mentioned under Acknowledgements.

Acknowledgements: Under Acknowledgements please specify contributors to the article other than the authors accredited. Please also include specifications of the source of funding for the study and any potential conflict of interests if appropriate. Suppliers of materials should be named and their location (town, state/county, country) included.

Ethical Approvals

Experimental Subjects

Experimentation involving human subjects will only be published if such research has been conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version, 2002 www.wma.net/e/policy/b3.htm) and the additional requirements, if any, of the country where the research has been carried out. Manuscripts must be accompanied by a statement that the research was undertaken with the understanding and written consent of each participant and according to the above mentioned principles. A statement regarding the fact that the study has been independently reviewed and approved by an ethical board should also be included. Editors reserve the right to reject papers if there are doubts as to whether appropriate procedures have been used.

All studies using human participants or animal subjects should include an explicit statement in the Material and Methods section identifying the review and ethics committee approval for each study, if applicable. Editors reserve the right to reject papers if there is doubt as to whether appropriate procedures have been used.

Ethics of investigation: Papers not in agreement with the guidelines of the Helsinki Declaration as revised in 1975 will not be accepted for publication.

Clinical Trials

Clinical trials should be reported using the CONSORT guidelines available at www.consort-statement.org. A CONSORT checklist should also be included in the submission material (http://www.consort-statement.org/mod_product/uploads/CONSORT 2001 checklist.doc).

Manuscripts reporting results from a clinical trial must provide the registration number and name of the clinical trial. Clinical trials can be registered in any of the following free, public clinical trials registries: www.clinicaltrials.gov, clinicaltrials-dev.ifpma.org/, isrctn.org/. The clinical trial registration number and name of the trial register will be published with the paper.

Conflict of Interest

Authors are required to disclose any possible conflict of interest. These include financial (for example patent, ownership, stock ownership, consultancies, speaker's fee). Author's conflict of interest (or information specifying the absence of conflicts of interest) will be published under a separate heading entitled 'Conflict of Interests'.

Journal of Intellectual Disability Research requires that sources of institutional, private and corporate financial support for the work within the manuscript must be fully acknowledged, and any potential conflicts of interest noted. Please include this information under the separate headings of 'Source of Funding' and 'Conflict of Interest' at the end of your manuscript.
If the author does not include a conflict of interest statement in the manuscript then the following statement will be included by default: "No conflicts of interest have been declared".

Source of Funding

Authors are required to specify the source of funding for their research when submitting a paper. Suppliers of materials should be named and their location (town, state/county, country) included. The information will be disclosed in the published article.

Publication Ethics

The journal is a member of, and subscribes to the principles of the Committee on Publication Ethics (COPE). Wiley's Ethics guidelines can also be found at http://exchanges.wiley.com/ethicsguidelines

3. MANUSCRIPT TYPES ACCEPTED

Original Research Articles

The main text should proceed through sections of Abstract, Background, Methods, Results, and Discussion. Reports of up to 4,500 words are suitable for major studies and presentation of related research projects or longitudinal enquiry of major theoretical and/or empirical conditions. Please note that articles exceeding 4,500 words will be unsubmitted immediately from the review process and the authors will be asked to reduce the length of the article.

Authors submitting articles should be guided by the following checklists prior to submission:

For observational studies: http://www.strobe-statement.org/?id=available-checklists
For diagnostic studies: (http://www.stard-statement.org/checklist_maintext.htm)

Qualitative Studies

Qualitative Studies are only considered if they have strong theoretical underpinnings and use an established method of data synthesis.

Systematic Reviews

The maximum word length for systematic reviews is 4,500 words. Authors submitting a systematic review are encouraged to assess the quality of their article against the PRISMA checklist prior to submission (http://www.prisma-statement.org/2.1.2 - PRISMA 2009 Checklist.pdf) or MOOSE guideline (insert link to MOOSE PdF). Further details on systematic reviews can be obtained from Prof. Richard Hastings (Editor); email: R.Hastings@warwick.ac.uk

Brief Reports

Brief Reports of up to 1,500 words are encouraged especially for replication studies, methodological research and technical contributions.

Annotation Articles

Annotation Articles should be no more than 5,500 words long including tables and figures and should not have been previously published or currently under review with another journal. The normal instructions to authors apply. The date

for submission of the article should be negotiated with the Editor in Chief. An honorarium of £400 in total shall be paid to the authors(s) when the article is accepted for publication.

Three main types of Annotations will be commissioned: 1. Authoritative reviews of empirical and theoretical literature. 2. Articles proposing a novel or modified theory or model. 3. Articles detailing a critical evaluation and summary of literature pertaining to the treatment of a specific disorder.

Hypothesis Papers

A Hypothesis Paper can be up to 2,500 words and no more than twenty key references. It aims to outline a significant advance in thinking that is testable and which challenges previously held concepts and theoretical perspectives. Hypothesis papers should be discussed with the Editor in Chief prior to submission.

Please note JIDR does not publish ***Case studies.***

4. PREPARATION OF THE MANUSCRIPT

Author Services

Prior to submission, we encourage you to browse the 'Author Resources' section of the Wiley 'Author Services' website: http://olabout.wiley.com/WileyCDA/Section/id-827998.html. This site includes useful information covering such topics as copyright matters, ethics and electronic artwork guidelines.

Writing for Search Engine Optimization

Optimize the search engine results for your paper, so people can find, read and ultimately cite your work. Simply read our best practice SEO tips – including information on making your title and abstract SEO-friendly, and choosing appropriate keywords.

Pre-submission English-language editing

Authors for whom English is a second language may choose to have their manuscript professionally edited before submission to improve the English. Visit our site to learn about the options. All services are paid for and arranged by the author. Please note using the Wiley English Language Editing Service does not guarantee that your paper will be accepted by this journal.

Spelling

• Spelling should conform to The Concise Oxford Dictionary of Current English.

• A high proportion of papers are submitted with the term 'behavior' as opposed to 'behaviour'; please use 'behaviour'.

• Where applicable the journal standard is to use words ending in –ise as opposed to –ize. For example, use 'analyse' 'standardise' as opposed to 'analyze' and 'standardize'

Units of measurements, symbols and abbreviations should conform with those in Units, Symbols and Abbreviations (1977) published and supplied by the Royal Society of Medicine. This specifies the use of SI units.

Terminology

It is important that the term 'intellectual disabilities' is used when preparing manuscripts. Please note that 'intellectual disability', as used in the journal, includes those conditions labelled mental deficiency, mental handicap, learning disability and mental retardation in some counties. The term 'person', 'people' or 'participant(s)' should be used as opposed to 'patient(s)'.

Optimising your paper on social media

If your paper is accepted for publication we would like to present three, headline style summary statements on our facebook and twitter feed. When you submit your article you will be asked to enter up to three short headlines (key statements) capture the importance of your paper.

MANUSCRIPT STRUCTURE

The manuscript should be submitted in separate files: title page; main text file; figures.

Title page

A 'Title Page' must be submitted as part of the submission process as a 'Supplementary File Not for Review. The title page should contain:

(i) a short informative title that contains the major key words. The title should not contain abbreviations (see Wiley's best practice SEO tips;
(ii) the full names of the authors;
(iii) the author's institutional affiliations at which the work was carried out;
(iv) the full postal and email address, plus telephone number, of the author to whom correspondence about the manuscript should be sent;
(v) acknowledgements;
(vi) conflict of interest statement.
The present address of any author, if different from that where the work was carried out, should be supplied in a footnote.

Acknowledgements

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Main text

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Moss T.J. & Austin G.E. (1980) Preatherosclerotic lesions in Down's syndrome. *Journal of Mental Deficiency Research* **24**, 137- 41.

Seltzer M. M. & Krauss M.W. (1994) Aging parents with co-resident adult children: the impact of lifelong caregiving. In: *Life Course Perspectives on Adulthood and Old Age* (eds M. M. Seltzer, M.W. Krauss & M. P. Janicki), pp. 3–18. American Association on Mental Retardation, Washington, DC.

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Appendix 3: Quality checklist

Quality Appraisal Checklist for Case Series Studies* Full checklist

Study objective		
1.	**Was the hypothesis/aim/objective of the study clearly stated?**	Yes ☐ Partial ☐ No ☐
Study design		
2.	**Was the study conducted prospectively?**	Yes ☐ Unclear ☐ No ☐
3.	**Were the cases collected in more than one centre?**	Yes ☐ Unclear ☐ No ☐
4.	**Were patients recruited consecutively?**	Yes ☐ Unclear ☐ No ☐
Study population		
5.	**Were the characteristics of the patients included in the study described?**	Yes ☐ Partial ☐ No ☐
6.	**Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?**	Yes ☐ Partial ☐ No ☐
7.	**Did patients enter the study at a similar point in the disease?**	Yes ☐ Unclear ☐ No ☐
Intervention and co-intervention		
8.	**Was the intervention of interest clearly described?**	Yes ☐ Partial ☐ No ☐
9.	**Were additional interventions (co-interventions) clearly described?**	Yes ☐ Partial ☐ No ☐

This checklist should be cited as: Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about

Outcome measure		
10.	**Were relevant outcome measures established a priori?**	Yes ☐ Partial ☐ No ☐
11.	**Were outcome assessors blinded to the intervention that patients received?**	Yes ☐ Unclear ☐ No ☐
12.	**Were the relevant outcomes measured using appropriate objective/subjective methods?**	Yes ☐ Partial ☐ No ☐
13.	**Were the relevant outcome measures made before and after the intervention?**	Yes ☐ Unclear ☐ No ☐
Statistical analysis		
14.	**Were the statistical tests used to assess the relevant outcomes appropriate?**	Yes ☐ Unclear ☐ No ☐
Results and conclusions		
15.	**Was follow-up long enough for important events and outcomes to occur?**	Yes ☐ Unclear ☐ No ☐
16.	**Were losses to follow-up reported?**	Yes ☐ Unclear ☐ No ☐
17.	**Did the study provided estimates of random variability in the data analysis of relevant outcomes?**	Yes ☐ Partial ☐ No ☐
18.	**Were the adverse events reported?**	Yes ☐ Partial ☐ No ☐
19.	**Were the conclusions of the study supported by results?**	Yes ☐ Unclear ☐ No ☐
Competing interests and sources of support		
20.	**Were both competing interests and sources of support for the study reported?**	Yes ☐ Partial ☐ No ☐

*Note: Assessor(s) may decide to remove from the checklist the items that are not applicable to their project.

Quality checklist tailored

Study objective	
1.	**Was the hypothesis/aim/objective of the study clearly stated?** **Yes**: The hypothesis/aim/objective of the study was clearly reported (includes patients, intervention and outcome). **Partial**: Only one or two components (patients, intervention, or outcome) were included. **No**: The hypothesis/aim/objective was not reported.
Study design	
2.	**Was the study conducted prospectively?** **Yes:** It was clearly stated that the study was conducted prospectively. **Unclear**: Unclear or no information was provided. **No:** The study clearly stated it was a retrospective study.
Study population	
5.	**Were the characteristics of the patients included in the study described?** **Yes**: All of the most relevant characteristics of the patients were reported (for example, number, age, gender, ethnicity, severity of disease/condition, comorbidity, or etiology). **Partial**: Some, but not all, of the most relevant characteristics were reported. **No**: Only the number of patients was reported. *Note: Assessor(s) should decide which aspects are important before using the checklist.*
6.	**Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?** **Yes**: Both inclusion and exclusion criteria were reported. **Partial**: Either the inclusion or exclusion criteria were reported. **No**: Neither inclusion nor exclusion criteria were reported. *Note: Assessor(s) should decide which aspects are important before using the checklist.*
Intervention and co-intervention	
8.	**Was the intervention of interest clearly described?** **Yes**: All of the most relevant characteristics of the intervention were reported (for example, dosage, frequency or duration of intervention, administration methods, technical parameters, or characteristics of a device). **Partial**: Some, but not all, of the most relevant characteristics were reported. **No**: Only the name of the intervention was reported. *Note: Assessor(s) should decide which aspects are important before using the checklist.*
Outcome measures	
10.	**Were relevant outcome measures established a priori?** **Yes**: All relevant outcome measures were stated in the introduction or methods section.

	Partial: Some, but not all, of the relevant outcome measures were stated in the introduction or method section. **No**: None of the relevant outcome measures were stated in the introduction or method section.
11.	**Were outcome assessors blinded to the intervention that patients received?** **Yes**: The relevant outcomes were assessed by individuals who were not aware of the intervention. Answer yes when blinding is not applicable or is unnecessary (for example, mortality). **Unclear**: The study did not report whether the outcome assessors were aware of the intervention. **No**: It was clearly stated or obvious from the context that the relevant outcomes were analyzed by individuals who were aware of the intervention provided to patients.
12.	**Were the relevant outcomes measured using appropriate objective/subjective methods?** **Yes**: All relevant outcomes were measured with appropriate methods. These measures can be objective (for example, gold standard tests or standardized clinical tests), subjective (for example, self-administered questionnaires, standardized forms, or patient symptoms interview forms), or both. **Partial**: Some, but not all, relevant outcomes were measured with appropriate methods. **No**: The methods used to measure the relevant outcomes were inappropriate. *Note: Assessor(s) should decide which methods are appropriate before using the checklist.*
13.	**Were the relevant outcome measures made before and after the intervention?** **Yes**: The relevant outcome measures were made pre- and post-intervention; or the baseline measurements were not possible (for example, death). **Unclear**: The study did not report when the outcome measures were made. **No**: The outcome measures were only made post-intervention.
Statistical analysis	
14.	**Were the statistical tests used to assess the relevant outcomes appropriate?** **Yes**: The statistical tests were used appropriately (for example, parametric test for normally distributed population vs. nonparametric test for non-Gaussian population). Answer yes if no statistical analysis was performed and reasons for this were stated. **Unclear**: The statistical tests were not described in the methods section of the study. **No**: The statistical tests used were inappropriate. *Note: Assessor(s) should decide which statistical tests are appropriate before using the checklist. Seek expert assistance if necessary.*
Results and conclusions	
15.	**Was follow-up long enough for important events and outcomes to occur?** **Yes**: It was clear from the information provided that the follow-up period was long enough for the majority (at least 80%) of patients, to allow for important events and outcomes (for example, changes in clinical status, adverse events) to occur. **Unclear**: The length of follow-up was not clearly reported. **No**: It is clear from the information provided that the follow-up period was not long enough to allow for important events and outcomes to occur.

	Note: Assessor(s) should define the appropriate duration of follow-up for each outcome of interest (for example, short-term and long-term adverse events).
17.	**Did the study provided estimates of random variability in the data analysis of relevant outcomes?** **Yes**: The estimates of the random variability (for example, standard error, standard deviation, confidence interval for normally distributed data or range and interquartile range for non-normally distributed data) were reported for all of the relevant outcomes or could be calculated from the raw data presented in the study. **Partial**: The estimates of the random variability were reported for some, but not all of the relevant outcomes. **No**: The estimates of the random variability were not reported for any of the relevant outcomes.
18.	**Were the adverse events reported?** **Yes**: The undesirable or unwanted events during the study period or within a pre-specified time period were reported; or the absence of adverse event(s) was mentioned in the study. **Partial**: Some, but not all, important adverse events were reported. **No**: There was no statement about the presence or absence of adverse events. *Note: Assessor(s) should decide which adverse events are most important. Seek clinical expert assistance if necessary.*
19.	**Were the conclusions of the study supported by the results?** **Yes**: The conclusions of the study were supported by the evidence presented in the results and discussion sections. **Unclear**: Unclear conclusion statement that makes it difficult to link the presented evidence to conclusions. **No**: The conclusions were not supported by the evidence presented in the results and discussion sections.
Competing interests and sources of support	
20.	**Were both competing interests and sources of support for the study reported?** **Yes**: Both competing interests and sources of support (financial or other) received for the study were reported; or the absence of any competing interest and source of support was acknowledged. **Partial**: Either the competing interest or source of support was reported. **No**: Neither competing interests nor sources of support were reported.

Appendix 4: Quality Ratings

No		Quality appraisal checklist item*															Summary
	Article	1	2	5	6	8	10	11	12	13	14	15	17	18	19	20	Out of 15
1	Sharpe & Ottenbacher (1990)	P	Y	Y	N	Y	N	U	Y	Y	Y	U	N	N	Y	N	8.5
	Second reviewer scores	Y	Y	Y	N	Y	N	N	Y	Y	P	P	N	N	Y	N	8
2	Sharpe (1992)	Y	Y	Y	N	Y	Y	N	Y	U	N	N	N	N	Y	N	7.5
3	Sullivan et al. (1995)	Y	Y	Y	N	P	N	N	N	U	N	Y	N	N	U	N	5.5
4	Evans & Meyer (1999)	P	Y	Y	N	N	Y	N	Y	Y	Y	Y	N	N	Y	N	8.5
5	Koppenhaver et al. (2001)	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	N	Y	N	9**
6	Yasuhara & Sugiyama (2001)	N	Y	Y	N	N	Y	N	N	N	N	Y	N	N	Y	N	5
	Second reviewer scores	Y	Y	Y	N	Y	N	N	N	N	N	Y	N	Y	Y	N	7
7	Hetzroni et al. (2002)	Y	Y	Y1	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	N	10**
8	Elefant & Lotan (2004)	N	Y	Y	N	Y	N	N	N	N	N	U	N	N	N	N	3.5
9	Lotan et al. (2004)	Y	Y	Y	P	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	10.5**
10	Elefant & Wigram (2005)	Y	U	Y	N	Y	Y	N	Y	Y	N	Y	N	N	N	N	7.5
11	Bergström-Isacsson (2007)	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	10**
	Second reviewer scores	Y	Y	Y	P	N	Y	N	Y	Y	Y	Y	Y	Y	Y	P	12
12	Fabio et al. (2011)	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	10**
13	Lotan et al. (2012)	Y	Y	N	N	P	Y	N	Y	Y	N	Y	N	N	Y	Y	8.5
14	Bartolotta & Remshifski (2012)	Y	Y	Y	N	Y	Y	N	Y	Y	N	N	N	N	N	Y	8
15	Fabio et al. (2013)	Y	Y	Y	N	Y	Y	N	P	Y	Y	U	N	N	Y	Y	10**
16	Stasolla & Caffò (2013)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	11**

	Second reviewer scores	Y	Y	Y	P	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	11.5
17	Hackett et al. (2013)	Y	N	Y	N	Y	Y	N	Y	N	Y	Y	Y	N	Y	N	9**
18	Stasolla et al. (2014)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	11**
19	Lancioni et al. (2014)	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	10**
20	Stasolla et al. (2015)	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	N	N	Y	N	9**
21	Simacek et al. (2016)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	11**
	Second reviewer scores	Y	Y	Y	P	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	12.5
22	Simacek et al. (2017)	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N	Y	Y	9**

**Items 3,4,7,9 & 16 omitted*
***Rated acceptable quality and included in the review*
Scoring criteria: P=Partial U=Unclear Y=Yes N=No N=0, P/U=0.5, Y=1

Appendix 5: Recruitment cover letter

Dear

We are writing to you, to see if you might be willing to help out with a research project into Rett Syndrome. This research will aim to help us understand more about diminished behaviors in Rett Syndrome, particularly during Rett episodes.

If you might be willing to take part, please look over the project information sheet and the research pack (enclosed). Please take the time to read the information sheet below which outlines why the research is being conducted and the details of involvement.

We would be delighted if you would be willing to take part in this research. Completing the questionnaires, should only take 20 minutes or you can complete them using the links provided. If you have any questions or concerns, please contact Annika Amoako using the contact details enclosed.

Many thanks for taking the time to read this,

Annika Amoako

Trainee Clinical Psychologist

Cardiff University

Dr Julian Hare

Research Director

Cardiff University

Appendix 6: Participant Information Sheet

Participant Information Sheet

Annika Amoako

Doctoral Programme in Clinical Psychology (11th Floor)

Tower Building

70 Park Place

Cardiff

CF10

Email: amoakoa@cardiff.ac.uk

Study title: The prevalence of attenuated behaviors in Rett Syndrome

What is the study?

We are researching the behaviors associated with Rett Syndrome, in particular the reduction in motor behaviors during 'Rett episodes'. The research project will help us gain a better understanding of the behaviors seen in Rett Syndrome and will inform future research into this area. This project has been reviewed and ethically approved by The Cardiff School of Psychology Ethics Committee.

Do I have to take part?

You do not have to take part in the research. If you do not want to take part or if you decide to withdraw from the research at a later date you can without having to provide a reason.

What do I have to do?

Complete some questionnaires about attenuated behaviours that you observe both during a Rett 'episode' and when your child is not experiencing a Rett 'episode'. These questionnaires can be completed and returned using the self-addressed envelope provided, via email or completed online.

If you would prefer to complete the study online, please use the following link: https://cardiffunipsych.eu.qualtrics.com/jfe/form/SV_7X2YxToNZq3tIoJ

Will be data be anonymous?

If you agree to take part in this study, the only identifiable information will be on the consent form. You will be asked to choose a unique 4 digit code that only you can identify your information by. For example the last four digits of your phone number. This is so that your information can be kept anonymously, but if you wish for your data to be removed at a later date the researcher can identify your data by this unique code. This will not be linked to the questionnaires once the questionnaires are inputted onto a database. To ensure your data is kept confidentially, the paper copies of your questionnaires will be kept in locked filing cabinets, however the data from the questionnaires will be kept anonymously. For the research study, I will have access to the information provided on the questionnaires. To ensure your data is anonymous, no identifiable data will be held electronically. Any information from the research programme will be stored on laptops and NHS computers and will not contain identifiable information.

The only circumstance in which we may pass on your details to another professional would be if you either tell us that you are planning on harming yourself or somebody else, or if you give us serious reason to believe that you intend to commit a crime. This is to keep you and others safe. If this happens, we will talk to you first before talking to anyone else and hopefully together we can decide on a course of action. I am working under the supervision of Dr Dougal Hare and, if I remain concerned about you I will also contact him for advice and to assist in deciding on any action.

What will happen to the results of the research study?

The results or the questionnaire will be written up and submitted as part of my Doctoral training in Clinical Psychology. The results may also be published in an academic journal and for academic presentations. It would not be possible to identify you within the study write up, because personal information will not be included in any publication of the results.

Are there any risks / benefits of taking part in the study?

We do not think there are any risks to taking part of the study. If you have any worries about taking part in the study, or any worries throughout the study please do not hesitate in contacting us using the details provided. Whilst there are no direct benefits to taking part, you will be helping an important research study which will contribute to the development of the understanding of Rett Syndrome in the future.

What if something goes wrong?

If you experience a problem or have concerns related to the study please do not hesitate to contact me, or either of my supervisors. If you would like to make a formal complaint, you can contact the Cardiff School of Psychology Ethics- Email: psychethics@cardiff.ac.uk, Telephone: +44 (0)29 2087 0360

I appreciate you taking the time to read this letter. If you have any questions, or would like more information about the research study, please contact:

Annika Amoako

Doctoral Programme in Clinical Psychology (11th Floor)

Tower Building

70 Park Place

Cardiff

CF10

Email: amoakoa@cardiff.ac.uk

Alternatively, you can speak to my research, Dr. Dougal Julian Hare who is the Research Director of the Cardiff University Clinical Psychology Doctorate on: Email: HareD@cardiff.ac.uk, Telephone: +44 (0)29 208 70582.

Many thanks for your time,

Ms. Annika Amoako

Trainee clinical psychologist

Appendix 7: Consent form

CONSENT FORM

Study Name: **The prevalence of attenuated behaviors in Rett Syndrome**

Please choose a unique 4 digit code that only you can identify your information by. For example the last four digits of your phone number. This is so that your information can be kept anonymously, but if you wish for your data to be removed at a later date the researcher can identify your data by this unique code. Please use the same code under participant number on all of the questionnaires.

Participant Number: _____

Please initial box

- I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
- I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. ☐
- I understand that I can refuse to answer any question I am asked without giving any reason. ☐
- I understand that once psychometrics are transferred electronically, any information I provide that can be used to identify me in this consent form will not be linked to my questionnaires when it is transferred electronically and therefore my data will be anonymized at that point. ☐
- I give permission for anonymised responses to be included in the thesis and in academic articles, posters and conferences. ☐
- I agree to take part in the above study. ☐

Name	Date	Signature

Appendix 8: Debrief request form

Following you participation in the study, we would like to send you a debriefing information sheet. If you would like us to send you this information, please provide contact details of the best method in which to contact you. This information will be kept confidentially not be linked to your questionnaires. Once we have sent the correspondence to you and will destroy your contact information securely.

Name: ……

Email: …….

Address: ……

…….

…….

Thank you for your assistance.

Appendix 9: Demographic questionnaire

Demographic 1 – Questions about you

Participant Number: _____

Please give your age: _____ years old

Please indicate your gender (Please tick the box which applies to you)

Male ☐ **Female** ☐

Please indicate your ethnicity (Please tick which ever box/boxes applies to you)

British ☐

Irish ☐

Other White ☐

White and Black Caribbean ☐

White and Black African ☐

White and Asian ☐

Any other mixed ☐

Indian ☐

Pakistani ☐

Bangladeshi ☐

Any other Asian ☐

Caribbean ☐

African ☐

Any other Black ☐

Chinese ☐

Other ethnic group ☐

Please indicate your relationship to the individual with Rett Syndrome:

Mother ☐ **Father** ☐

Demographic 2 – Questions about your child

Participant Number: _____

Please provide the age of your child: _____ years old

Please indicate their gender (Please tick the box which applies to your child)

Male ☐ **Female** ☐

Please indicate their ethnicity (Please tick which ever box/boxes applies to you)

British ☐

Irish ☐

Other White ☐

White and Black Caribbean ☐

White and Black African ☐

White and Asian ☐

Any other mixed ☐

Indian ☐

Pakistani ☐

Bangladeshi ☐

Any other Asian ☐

Caribbean ☐

African ☐

Any other Black ☐

Chinese ☐

Other ethnic group ☐

What is your child's current living circumstances?

Live with carer ☐

Live with other (not carer) ☐

Live with family (i.e with parents) ☐

Appendix 10: Rett episode questionnaire

Rett Episodes Questionnaire 3

Does your child have odd episodes of any sort? Such as seizures, episodes with disturbed breathing, or other episodes with altered awareness.

Yes ☐ **No** ☐ **Unsure** ☐

If yes or unsure, please provide as much detail as possible about these episodes. For example, do they look like seizures, episodes with disturbed breathing, or other episodes with altered awareness? Does your child change color? Does she appear agitated, calm or distressed?

How many different types of episodes does your child have? How often? How long? When did they first start having them?

Appendix 11: Attenuated Behaviour Questionnaire

Attenuated Behaviour Questionaire

This questionnaire asks about a number of different behaviours that your child/ the person you care for might show or may have shown in the past.

Each question describes a behaviour and then asks you to say whether your child/ the person you care for currently shows that behaviour and how this compares to what the behaviour was like in the past. For some of the questions you will also be asked to rate how often the behaviour happens and how severely it affects them.

For some of the items examples are given to help you think about what that behaviour might look like.

Please read each of the definitions and examples and then circle your response.

***** Please complete with the Rett 'episodes' in mind ***** (This will be completed second with half of the participants)

PART A: CORE SYMPTOMS

Question no.	Description	Please circle one answer				
1	**Are there times when he/she is very still for long periods of time, almost like a statue?**	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 2					
1a)	How often does the individual experience these periods of stillness at the moment?	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
1b)	How severely does the individual experience these periods of stillness at the moment?	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	
2	**Does he/she seem to get 'stuck' when trying to do something?** (e.g. stopping mid-air half way through reaching for something & looking like they are trying to move but can't OR beginning to pick up a cup to drink but lifting it only half way and then putting it down again)	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 3					
2a)	How often does the individual experience these periods of 'stuckness' at the moment?	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	

2b)	How <u>severely</u> does the individual experience these periods of 'stuckness' <u>at the moment?</u>	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	
3	**Does he/she seem to find it difficult to stop doing actions once they have started them?** (e.g. repeatedly putting a coat on & taking it off again & again for a long period of time)	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 4					

Question no.	Description	Please circle one answer				
3a)	How often does the individual experience these periods of problems stopping actions <u>at the moment?</u>	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
3b)	How <u>severely</u> does the individual experience these periods of problems stopping actions <u>at the moment?</u>	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	
4	**Does he/she seem to find it difficult to start moving?** (e.g. lying still and looking like he/she wants to get up or reach for something but can't)	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 5					
4a)	How often does the individual experience these periods of difficulty initiating movement <u>at the moment?</u>	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
4b)	How <u>severely</u> does the individual experience these periods of difficulty initiating movement <u>at the moment?</u>	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	
5	**Does he/she move very slowly and takes a long time to finish actions?** (e.g. moving very slowly when doing things like picking up a cup to drink or eating dinner)	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No-never*
	If you answered 'No' go to Question 6					
5a)	How often does the individual experience these periods of slowness in movement <u>at the moment?</u>	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
5b)	How <u>severely</u> does the individual experience these periods of slowness in movement <u>at the moment?</u>	*Very severely* (they seem unable to focus on or do	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	

		anything else at this time)				
6	**Are there times when he/she needs physical OR verbal prompts to complete actions?** (e.g. needing someone to tell them or touch their arm to enable them to lift a cup to their mouth to drink) ***If you answered 'No' go to Question 7***	*Yes more than before*	*Yes the same as before*	*Yes but less than before*	*No – not at the moment but it used to happen*	*No- never*
6a)	How often does the individual experience these periods of requiring prompts to complete actions <u>at the moment?</u>	*All/almost all the time they are awake*	*Most of the time they are awake*	*Some of the time they are awake*	*Rarely when they are awake*	
6b)	How <u>severely</u> does the individual experience these periods of requiring prompts to complete actions <u>at the moment?</u>	*Very severely* (they seem unable to focus on or do anything else at this time)	*Quite severely* (it is difficult for them to focus on or do anything else at this time)	*Moderately* (there seems to be an effect on their ability to focus on or do things)	*Slightly* (this seems to have little or no effect on their life)	

PART B: OTHER RELATED BEHAVIOURS AND SYMPTOMS

Question no.		Yes more than before	Yes the same as before	Yes but less than before	No – not at the moment but it used to happen	No -never
7	**Does he/she like to move their body in repetitive ways?** (This includes any frequent body movement such as body rocking, twisting wrists, flicking fingers etc?)	**5**	**4**	**3**	**2**	**1**
8	**Does he/she strike and hold stiff poses?**	**5**	**4**	**3**	**2**	**1**
9	**Does he/she experiences 'tics' (speech or movement)?** (e.g. suddenly & repetitively move their body or saying a word/phrase in a way they seem unable to control?)	**5**	**4**	**3**	**2**	**1**
10	**Does he/she move their hands or feet in an odd way?** (e.g. twisting, waving or shaking)	**5**	**4**	**3**	**2**	**1**
11	**Does he/she twist or flick their hands in front of their eyes?**	**5**	**4**	**3**	**2**	**1**
12	**Does he/she move in a very jerky way?**	**5**	**4**	**3**	**2**	**1**
13	**Does he/she walk unusually?**	**5**	**4**	**3**	**2**	**1**
14	**Does he/she display examples of mood changeability internally? (e.g. has he/she lost enjoyment in their favourite activities? <u>OR</u> Withdraws from others?)**	**5**	**4**	**3**	**2**	**1**
15	**Does he/she display examples of mood changeability externally?** (e.g. does he/she scream, cry or laugh suddenly for no reason? OR Behave aggressively towards themselves or others at times? OR Displays impulsive or excitable phases?)	**5**	**4**	**3**	**2**	**1**
16	**Does he/she find it difficult to walk through doorways?**	**5**	**4**	**3**	**2**	**1**
17	**Does he/she find it difficult to walk across lines on the floor or changes in flooring?** (e.g. from a carpet to a wooden floor)	**5**	**4**	**3**	**2**	**1**
18	**Is he/she doing less than they used to?** (e.g. is it harder than it used to be to encourage them to do activities?)	**5**	**4**	**3**	**2**	**1**
19	**Are there periods where he/she communicates with others less or not at all?** (This includes all communication methods - it could be reduced speech or other communication such as signing, PECS etc)	**5**	**4**	**3**	**2**	**1**

20	**Are there periods where he/she is incontinent OR refuses to use the toilet when they used to?** (e.g. the person is not using skills that they have used in the past and are soiling themselves when they would use the toilet before)	**5**	**4**	**3**	**2**	**1**
21	**Does he/she have sleep problems?** (e.g. finds it difficult to get to sleep at night, wants to sleep in the day but not at night, gets little sleep etc.)	**5**	**4**	**3**	**2**	**1**
22	**Are there periods where he/she refuses to eat OR eats less than they used to?**	**5**	**4**	**3**	**2**	**1**
23	**Does he/she move or roll their eyes unusually?** (e.g. rolls their eyes around again & again or looks from left to right again & again)	**5**	**4**	**3**	**2**	**1**
24	**Does he/she pull unusual facial expressions or 'grimaces'?**	**5**	**4**	**3**	**2**	**1**
25	**Does he/she ignore instructions?** (This must be for instructions that you know the individual understands)	**5**	**4**	**3**	**2**	**1**
26	**Does he/she refuse to wash or change his/her clothes?**	**5**	**4**	**3**	**2**	**1**
27	**Does he/she make groaning or other unusual noises regularly?**	**5**	**4**	**3**	**2**	**1**
28	**Does he/she stare into space or fix their gaze onto certain things?**	**5**	**4**	**3**	**2**	**1**

Appendix 12: Study debrief form and useful contacts

Study Debriefing and Useful contacts

Thank you for taking part in this study- your participation was greatly appreciated. The project is exploring the prevalence of attenuated behavior in Rett Syndrome. We were interested in this to increase our understanding about Rett Syndrome, specifically during 'Rett Episodes'. The more professionals know about Rett Syndrome, your child's experience of it the more they can try to improve the level of care they are offering. Furthermore, any research in the area can contribute to increasing awareness of the syndrome in the public domain. It is our hope that the results of this research, which will all be anonymised, can be presented as a poster at various health conferences to promote awareness. Additionally, we would also like to write the project as a paper for publication in a scientific journal.

Useful Contacts

If you feel upset or low after taking part here are some suggestions as to sources of support you may wish to consider:

1. Your partner, friends and family may be able to provide you with immediate support.
2. Your GP particularly if you remain upset about what has been discussed for longer than you feel comfortable with. Your GP may also have a counsellor attached to the surgery who would be able to assist, or could refer you to an Increased Access to Psychological Therapies Service (within England). You may also be able to self refer to your local IAPT service.
3. Alternatively you can contact the project supervisor, Dr. Dougal Julian Hare who is the Research Director of the Cardiff University Clinical Psychology Doctorate on: Email: HareD@cardiff.ac.uk, Telephone: +44 (0)29 208 70582.

***If you feel at risk of harming yourself or others or at risk of taking your own life then please call your local crisis team or the Samaritans for help (see numbers below). If you are unable to contact the latter organisations then please call the emergency services for an immediate response.**

- The Samaritans 116 123 (UK- Free to call)
- Alternatively, call your local community mental health team or local crisis team number

Other support lines:

- SANEline, a specialist mental health helpline - 0300 304 7000 between 6pm and 11pm each evening (local-rate)
- NHS Line- call 111 (Free to call)

Appendix 13: Rett UK correspondence letter

Hello Annika,

Thank you for contacting us.

We would be very happy to help you with your study by raising awareness and contacting families who are known to us.

We do have a quarterly newsletter, the next of which is due to be circulated mid/end June and if you would like to put something in this edition to explain to families what you will be doing and how they can help, that may be a good starting point.

We can also contact families directly on your behalf when you are ready.

Please give me a call anytime if you would like to talk through your project and our potential involvement

Best wishes

Julie

Julie Benson
Family Support Manager
Tel: 01582 798911
Mobile: 07557 850025
Professional support for families affected by Rett syndrome Text RETT01 £5 to 70070

Rett UK
Langham House West
Mill Street
Luton
LU1 2NA

-----Original Message-----
From: Annika Amoako [mailto:AmoakoA@cardiff.ac.uk]
Sent: 22 March 2016 09:44

To: Julie Benson <julie.benson@rettuk.org>
Subject: Fw: Clinical Psychology trainee and research in Rett Syndrome

Dear Julie,

I hope you do not mind me contacting you directly. As per previous correspondence with Angus Clarke, I am a second year trainee in Clinical Psychology at Cardiff University, interested in researching Rett Syndrome. I was very keen on the project Angus proposed using eye gaze technology, however after further meetings with my supervisor it has been felt that this project would be too large given my time scales.

Therefore I am currently in the process of submitting an ethics proposal to the University with my supervisor, Dr Julian Hare, Research Director, Cardiff University. The proposed study will investigate attenuated behaviours in Rett Syndrome, specifically during Rett Episodes. This will be conducted by asking parents to complete a questionnaire. I will also be conducting a systematic review into the research literature of Rett Syndrome. I am still in the process of finalising the specific topic, but I am hoping to conduct the systematic review into interventions for Rett Syndrome.

Therefore at this early stage, I wondered if there might be any opportunity for recruitment links for the project to be signposted Rett UK via platforms such as social media or your news letter.

I would greatly appreciate any support Rett UK could offer and would gladly answer any questions regarding the research.

Many thanks for your time and apologies if you are not the right contact within Rett UK for this enquiry to be directed to.

Annika Amoako
Trainee Clinical Psychologist

Appendix 14: Ethics approval confirmation

School of Psychology
Head of School Professor Petroc Sumner BA MA PhD
Ysgol Seicoleg
Pennaeth yr Ysgol Yr Athro Petroc Sumner BA MA PhD

Cardiff University
Tower Building
70 Park Place
Cardiff CF10 3AT
Wales UK
Tel *Ffôn* +44(0)29 2087 4007
www.psych.cf.ac.uk
Prifysgol Caerdydd
Adeilad y Tŵr
70 Plas y Parc
Caerdydd CF10 3AT
Cymru Y Deyrnas Unedig

Ref: EC.16.05.10.4513R

4th July 2016

Dear Annika Amoako,

The Ethics Committee has considered your revised research project proposal: The prevalence of attenuated behaviours in Rett Syndrome (EC.16.05.10.4513R).

The project was approved on 31st May.

Please note that if any changes are required for the above project then you must submit an amendment for review by the Ethics Committee.

Yours sincerely,

Mark Jones
School of Psychology Research Ethics Committee
02920 870360
psychethics@cf.ac.uk

Appendix 15: Ethics addendum approval confirmation

Reply all

Thu 09/03, 11:35

Annika Amoako;

Dougal Hare

Inbox

You forwarded this message on 21/03/2017 11:23

Action Items

Dear Annika,

The Ethics Committee has considered the amendment to your PG project proposal: The prevalence of attenuated behaviours in Rett Syndrome (EC.16.05.10.4513RA).

The amendment has been approved.

Please note that if any changes are made to the above project then you must notify the Ethics Committee.

Best wishes,
Mark Jones

Appendix 16: SPSS output

A) Systematic Review

1. Interrater Agreement KAPPA

Reviewer_1 * Reviewer_2 Crosstabulation

Count

		Reviewer_2			
		No	Partial / Unclear	Yes	Total
Reviewer_1	No	18	2	8	28
	Partial / Unclear	1	1	1	3
	Yes	2	3	39	44
Total		21	6	48	75

Symmetric Measures

		Value	Asymptotic Standardized Error[a]	Approximate T[b]	Approximate Significance
Measure of Agreement	Kappa	.561	.086	5.804	.000
N of Valid Cases		75			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

B) Empirical Paper

1. Descriptive and tests for normal distribution for age

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Age_carer	31	93.9%	2	6.1%	33	100.0%
Age_child	31	93.9%	2	6.1%	33	100.0%

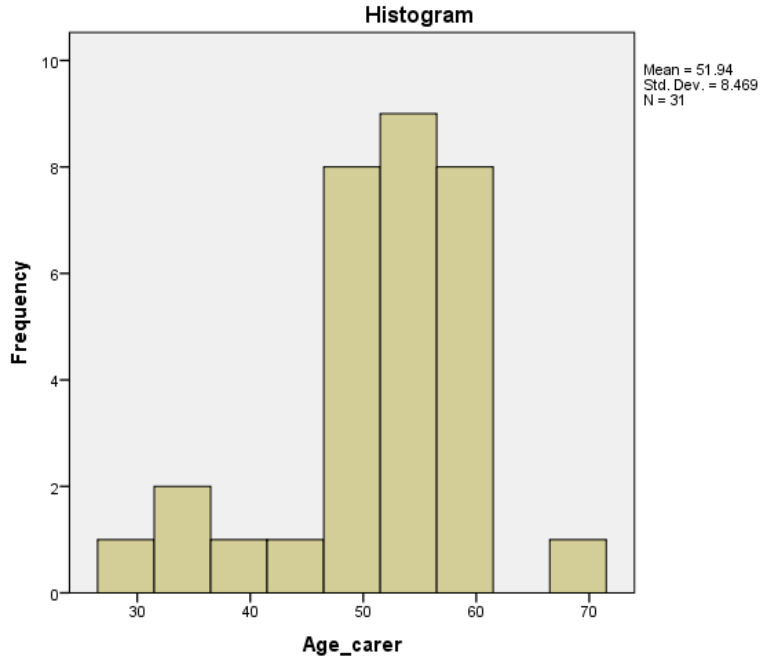
Descriptives

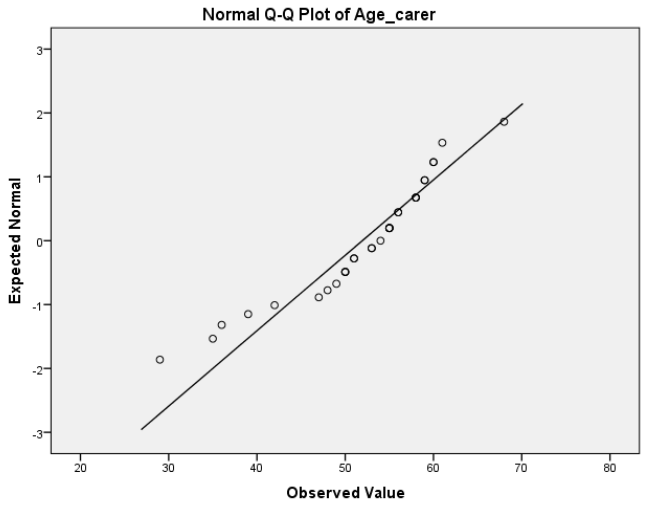
			Statistic	Std. Error
Age_carer	Mean		51.94	1.521
	95% Confidence Interval for Mean	Lower Bound	48.83	
		Upper Bound	55.04	
	5% Trimmed Mean		52.34	
	Median		54.00	
	Variance		71.729	
	Std. Deviation		8.469	
	Minimum		29	
	Maximum		68	
	Range		39	
	Interquartile Range		9	
	Skewness		-.984	.421
	Kurtosis		1.059	.821
Age_child	Mean		18.71	1.316
	95% Confidence Interval for Mean	Lower Bound	16.02	
		Upper Bound	21.40	
	5% Trimmed Mean		19.03	
	Median		21.00	
	Variance		53.680	
	Std. Deviation		7.327	
	Minimum		2	
	Maximum		29	
	Range		27	
	Interquartile Range		11	
	Skewness		-.564	.421
	Kurtosis		-.477	.821

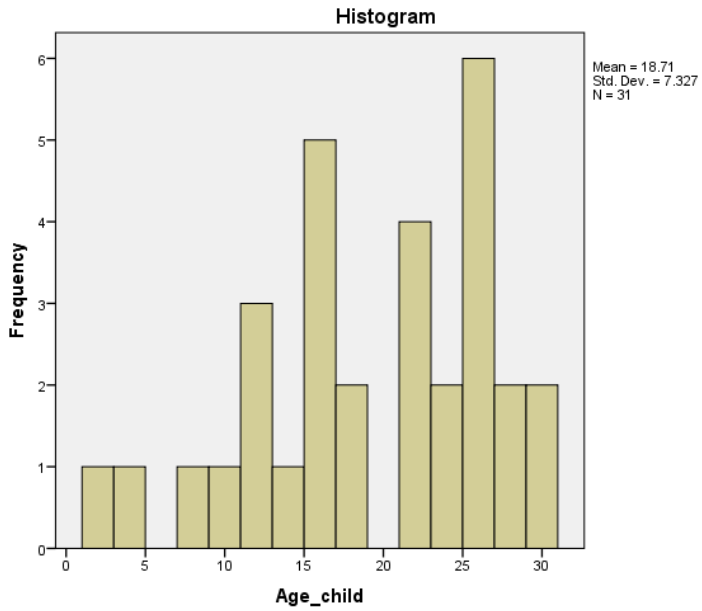
Tests of Normality

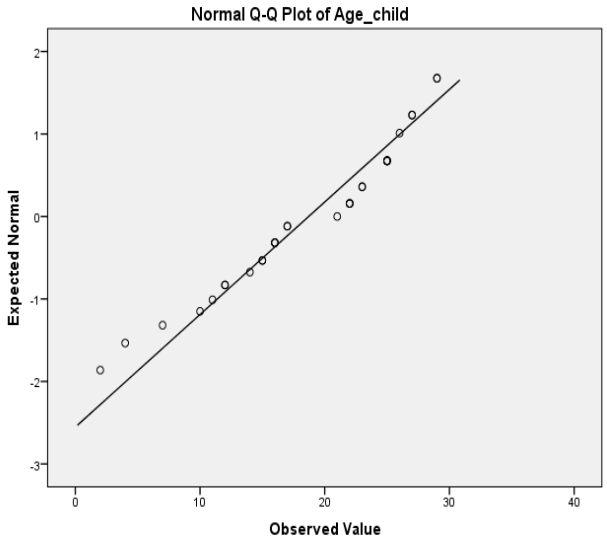
	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age_carer	.152	31	.068	.921	31	.024
Age_child	.157	31	.049	.941	31	.086

a. Lilliefors Significance Correction

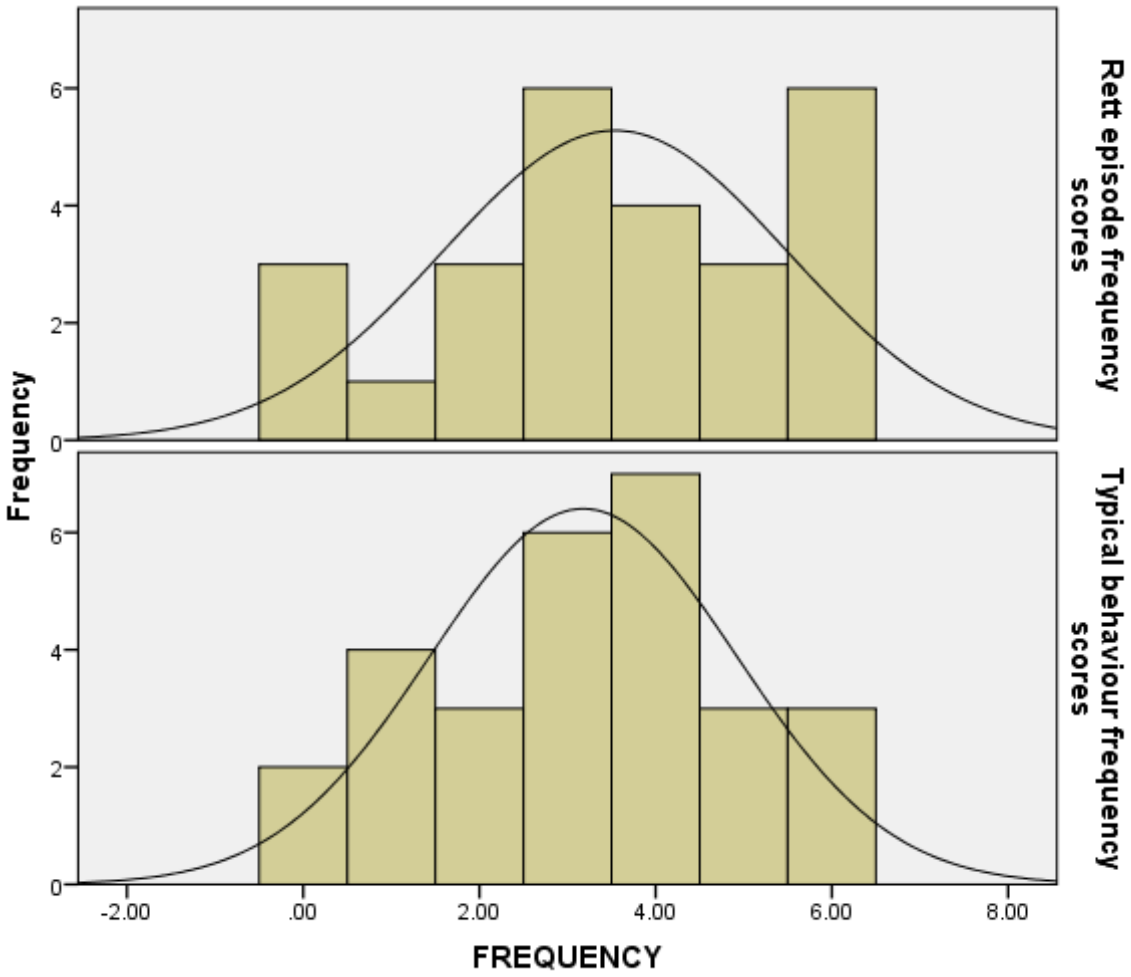


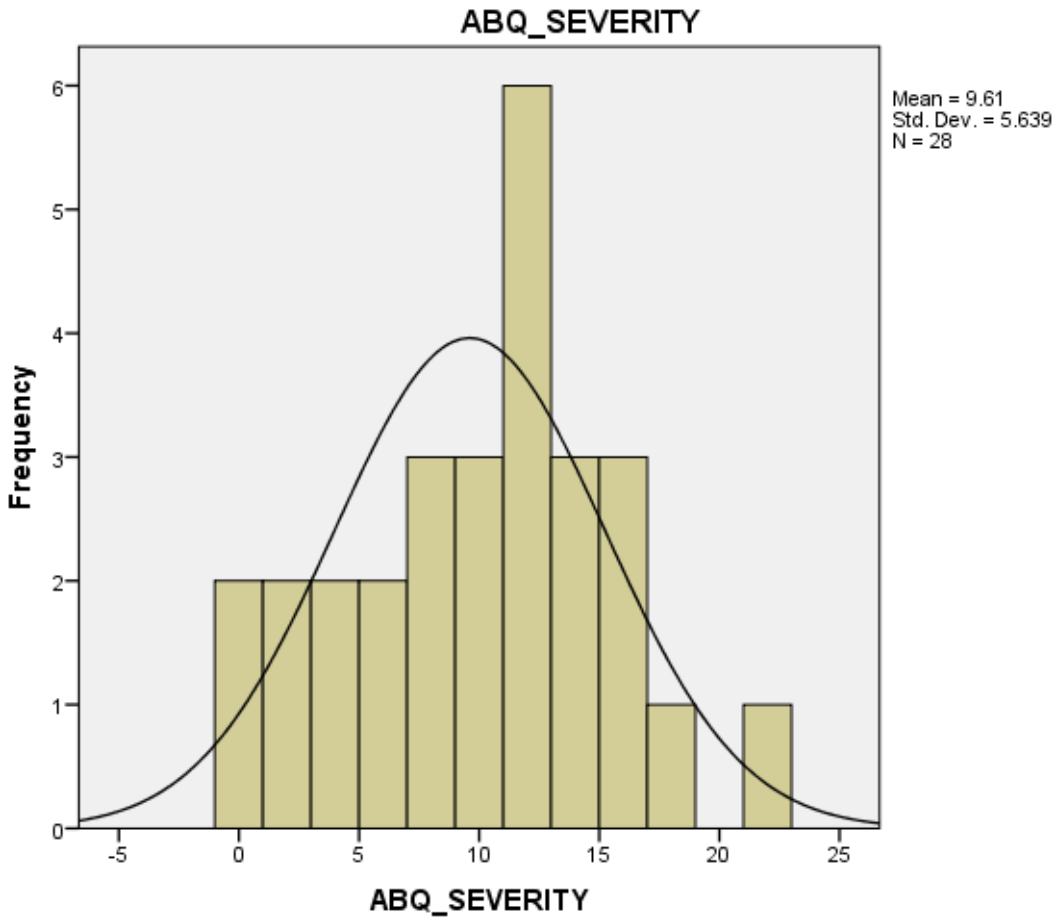


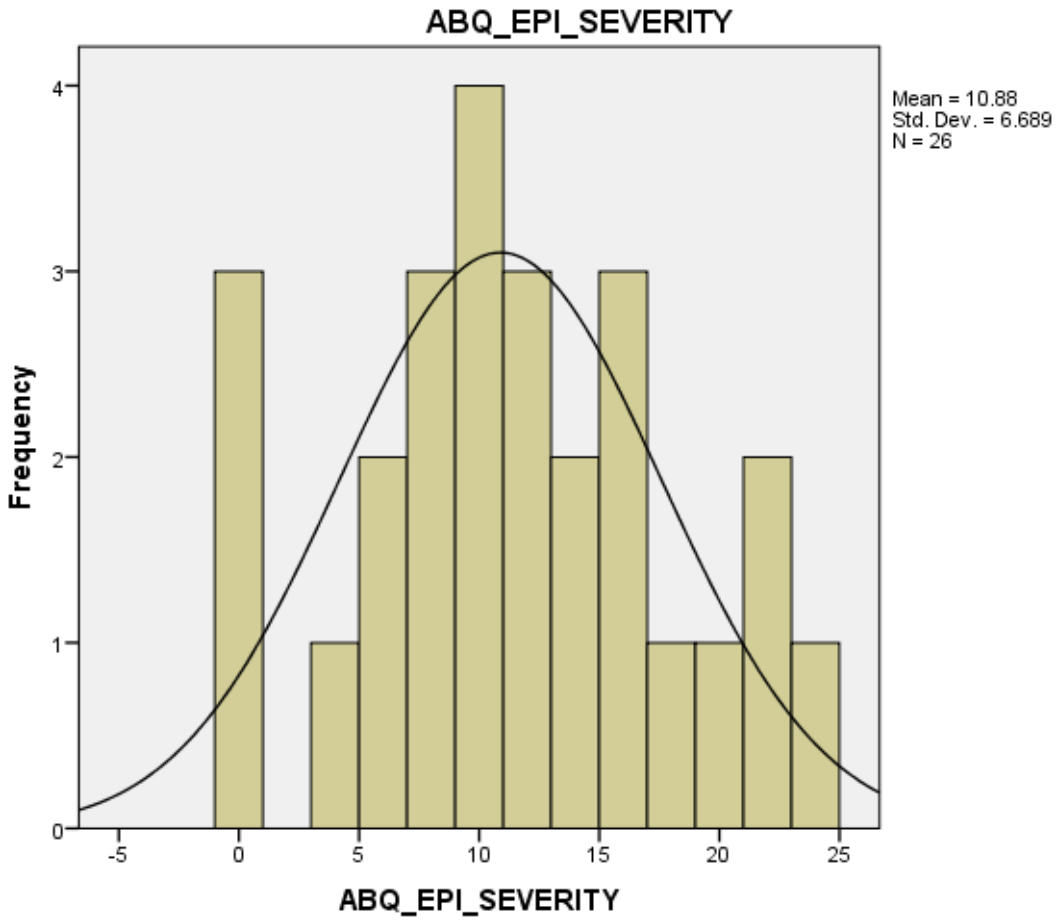

Histogram
Mean = 18.71
Std. Dev. = 7.327
N = 31
Frequency
Age_child


Normal Q-Q Plot of Age_child
Expected Normal
Observed Value

2. Core symptom frequency and severity




ABQ_SEVERITY
Mean = 9.61
Std. Dev. = 5.639
N = 28
Frequency
0
1
2
3
4
5
6
-5
0
5
10
15
20
25
ABQ_SEVERITY



3. Homogeneity of variance test for frequency of core scores and severity

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
ABQ_SEVERITY	26	92.9%	2	7.1%	28	100.0%
ABQ_FREQ	26	92.9%	2	7.1%	28	100.0%
ABQ_EPI_SEVERITY	26	92.9%	2	7.1%	28	100.0%
ABQ_EPI_FREQ	26	92.9%	2	7.1%	28	100.0%

Descriptives

			Statistic	Std. Error
ABQ_SEVERITY	Mean		9.81	1.118
	95% Confidence Interval for Mean	Lower Bound	7.51	
		Upper Bound	12.11	
	5% Trimmed Mean		9.73	

	Median		11.00	
	Variance		32.482	
	Std. Deviation		5.699	
	Minimum		0	
	Maximum		22	
	Range		22	
	Interquartile Range		8	
	Skewness		-.042	.456
	Kurtosis		-.498	.887
ABQ_FREQ	Mean		3.27	.344
	95% Confidence Interval for Mean	Lower Bound	2.56	
		Upper Bound	3.98	
	5% Trimmed Mean		3.30	
	Median		3.50	
	Variance		3.085	
	Std. Deviation		1.756	
	Minimum		0	
	Maximum		6	
	Range		6	
	Interquartile Range		2	
	Skewness		-.254	.456
	Kurtosis		-.662	.887
ABQ_EPI_SEVERITY	Mean		10.88	1.312
	95% Confidence Interval for Mean	Lower Bound	8.18	
		Upper Bound	13.59	
	5% Trimmed Mean		10.83	
	Median		10.50	
	Variance		44.746	
	Std. Deviation		6.689	
	Minimum		0	
	Maximum		23	
	Range		23	
	Interquartile Range		10	
	Skewness		.072	.456
	Kurtosis		-.728	.887
ABQ_EPI_FREQ	Mean		3.54	.385
	95% Confidence Interval for Mean	Lower Bound	2.75	
		Upper Bound	4.33	
	5% Trimmed Mean		3.60	
	Median		3.50	

Variance	3.858	
Std. Deviation	1.964	
Minimum	0	
Maximum	6	
Range	6	
Interquartile Range	3	
Skewness	-.354	.456
Kurtosis	-.789	.887

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
ABQ_SEVERITY	.150	26	.138	.972	26	.663
ABQ_FREQ	.161	26	.080	.944	26	.169
ABQ_EPI_SEVERITY	.072	26	.200*	.968	26	.583
ABQ_EPI_FREQ	.126	26	.200*	.912	26	.029

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

4. Paired t-test with bootstrapping for Rett Episodes and everyday behaviour for severity.

Paired Samples Statistics

				Bootstrap[a]			
						95% Confidence Interval	
			Statistic	Bias	Std. Error	Lower	Upper
Pair 1	ABQ_EPI_SEVERITY	Mean	10.88	-.04	1.32	8.15	13.38
		N	26				
		Std. Deviation	6.689	-.162	.715	5.123	7.856
		Std. Error Mean	1.312				
	ABQ_SEVERITY	Mean	9.81	-.02	1.11	7.54	12.00
		N	26				
		Std. Deviation	5.699	-.152	.664	4.157	6.845
		Std. Error Mean	1.118				

a. Unless otherwise noted, bootstrap results are based on 2000 bootstrap samples

Paired Samples Correlations

		N	Correlation	Sig.	Bootstrap for Correlation[a]			
					Bias	Std. Error	95% Confidence Interval	
							Lower	Upper
Pair 1	ABQ_EPI_SEVERITY & ABQ_SEVERITY	26	.798	.000	-.004	.084	.600	.921

a. Unless otherwise noted, bootstrap results are based on 2000 bootstrap samples

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	ABQ_EPI_FREQ - ABQ_FREQ	.269	1.116	.219	-.181	.720	1.231	25	.230
Pair 2	ABQ_EPI_SEVERITY - ABQ_SEVERITY	1.077	4.049	.794	-.558	2.712	1.356	25	.187

Bootstrap for Paired Samples Test

			Bootstrap[a]				
						95% Confidence Interval	
		Mean	Bias	Std. Error	Sig. (2-tailed)	Lower	Upper
Pair 1	ABQ_EPI_SEVERITY - ABQ_SEVERITY	1.077	-.020	.793	.202	-.537	2.577

a. Unless otherwise noted, bootstrap results are based on 2000 bootstrap samples

4. The Wilcoxon Signed Rank Test for frequency scores

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
ABQ_FREQ	28	3.18	1.744	0	6	2.00	3.00	4.00
ABQ_EPI_FREQ	26	3.54	1.964	0	6	2.00	3.50	5.25

Ranks

		N	Mean Rank	Sum of Ranks
ABQ_EPI_FREQ - ABQ_FREQ	Negative Ranks	3[a]	9.33	28.00
	Positive Ranks	10[b]	6.30	63.00
	Ties	13[c]		
	Total	26		

a. ABQ_EPI_FREQ < ABQ_FREQ

b. ABQ_EPI_FREQ > ABQ_FREQ

c. ABQ_EPI_FREQ = ABQ_FREQ

Test Statistics[a]

	ABQ_EPI_FREQ - ABQ_FREQ
Z	-1.260[b]
Asymp. Sig. (2-tailed)	.208

a. Wilcoxon Signed Ranks Test

b. Based on negative ranks.

5. Bootstrapping for frequency scores

Paired Samples Statistics

				Bootstrap[a]			
						95% Confidence Interval	
			Statistic	Bias	Std. Error	Lower	Upper
Pair 1	ABQ_EPI_FREQ	Mean	3.54	.01	.38	2.81	4.27
		N	26				
		Std. Deviation	1.964	-.045	.209	1.472	2.285
		Std. Error Mean	.385				
	ABQ_FREQ	Mean	3.27	.01	.34	2.62	3.92
		N	26				
		Std. Deviation	1.756	-.040	.202	1.299	2.098
		Std. Error Mean	.344				

a. Unless otherwise noted, bootstrap results are based on 2000 bootstrap samples

Paired Samples Correlations

		N	Correlation	Sig.	Bootstrap for Correlation[a]			
					Bias	Std. Error	95% Confidence Interval	
							Lower	Upper
Pair 1	ABQ_EPI_FREQ & ABQ_FREQ	26	.826	.000	-.002	.082	.621	.944

a. Unless otherwise noted, bootstrap results are based on 2000 bootstrap samples

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	ABQ_EPI_FREQ - ABQ_FREQ	.269	1.116	.219	-.181	.720	1.231	25	.230

Bootstrap for Paired Samples Test

		Mean	Bootstrap[a]				
			Bias	Std. Error	Sig. (2-tailed)	95% Confidence Interval	
						Lower	Upper
Pair 1	ABQ_EPI_FREQ - ABQ_FREQ	.269	-.001	.214	.239	-.192	.654

a. Unless otherwise noted, bootstrap results are based on 2000 bootstrap samples

6. McNemars test for differences in prevalence of attenuated behaviours (3 or more core symptoms)

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
ABQ_EPI_THRESHOLD * ABQ_THRESHOLD	26	92.9%	2	7.1%	28	100.0%

ABQ_EPI_THRESHOLD * ABQ_THRESHOLD Crosstabulation

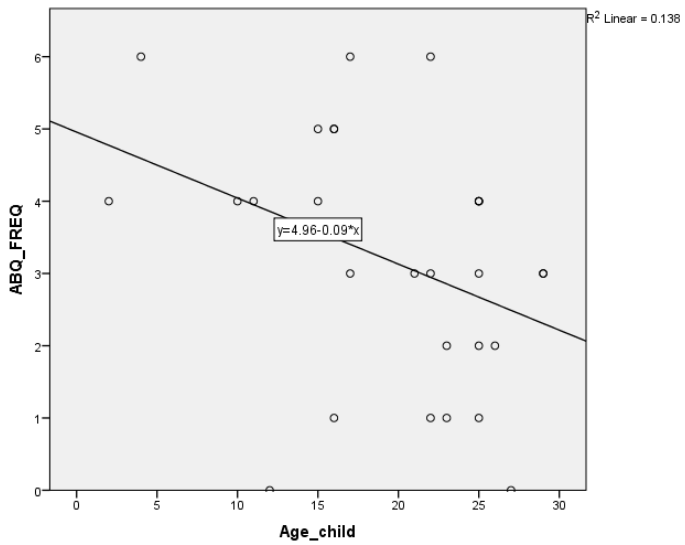
			ABQ_THRESHOLD		
			Meets threshold	Under threshold	Total
ABQ_EPI_THRESHOLD	Meets threshold	Count	17	3	20
		% within ABQ_EPI_THRESHOLD	85.0%	15.0%	100.0%
		% within ABQ_THRESHOLD	100.0%	33.3%	76.9%
	Under threshold	Count	0	6	6
		% within ABQ_EPI_THRESHOLD	0.0%	100.0%	100.0%
		% within ABQ_THRESHOLD	0.0%	66.7%	23.1%
Total		Count	17	9	26
		% within ABQ_EPI_THRESHOLD	65.4%	34.6%	100.0%
		% within ABQ_THRESHOLD	100.0%	100.0%	100.0%

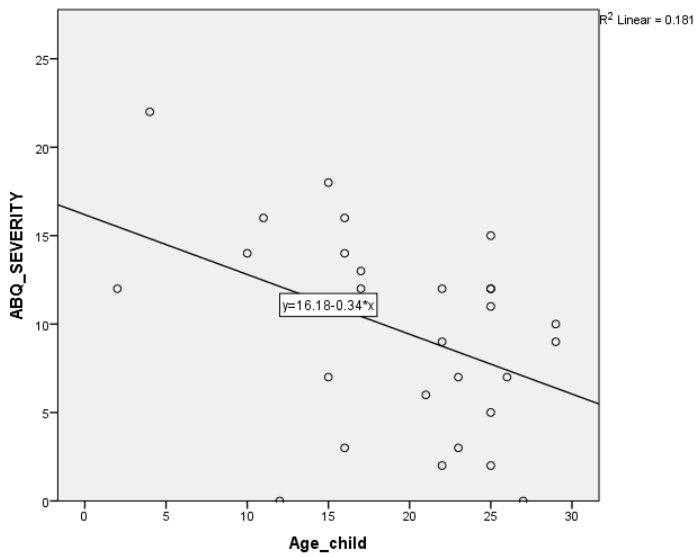
Chi-Square Tests

	Value	Exact Sig. (2-sided)
McNemar Test		.250[a]
N of Valid Cases	26	

a. Binomial distribution used.

7. Correlations for age and ABQ scores using scatter plots and Pearson's correlation co-efficient





Correlations

				Age_child	ABQ_FREQ	ABQ_SEVERITY
Age_child	Pearson Correlation			1	-.372	-.425*
	Sig. (2-tailed)				.051	.024
	N			28	28	28
	Bootstrap[c]	Bias		0	.004	.015
		Std. Error		0	.162	.177
		95% Confidence Interval	Lower	1	-.647	-.709
			Upper	1	-.016	-.026
ABQ_FREQ	Pearson Correlation			-.372	1	.896**
	Sig. (2-tailed)			.051		.000
	N			28	28	28
	Bootstrap[c]	Bias		.004	0	-.001
		Std. Error		.162	0	.042
		95% Confidence Interval	Lower	-.647	1	.795
			Upper	-.016	1	.967
ABQ_SEVERITY	Pearson Correlation			-.425*	.896**	1
	Sig. (2-tailed)			.024	.000	
	N			28	28	28
	Bootstrap[c]	Bias		.015	-.001	0
		Std. Error		.177	.042	0
		95% Confidence Interval	Lower	-.709	.795	1
			Upper	-.026	.967	1

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

c. Unless otherwise noted, bootstrap results are based on 2000 bootstrap samples