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# Ageing in Rett syndrome

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*Key words*: Intellectual disabilities, Rett syndrome, ageing

**Abstract**

*Background* The aim was to gain a UK national sample of people with Rett syndrome across the age range and (a) conduct a cross-sectional comparison of age groups and (b) undertake a longitudinal follow-up.

*Methods* From 308 potential participants approached to take part, a sample of 91 girls and women was achieved (29.5%). Their ages ranged from 4 to 47 years and 71were known to have a mutation in the *MECP2* gene. Seventy-two of the initial sample were followed-up 16 months later and 50 returned completed assessments (69.4%). Their ages ranged from 7 to 48 years and 42 were *MECP2* positive. Parental questionnaire measures of Rett syndrome specific characteristics, impulsivity, overactivity, mood, interest and pleasure, repetitive behaviour and self-injury were administered.

*Results* Adaptive behaviour and behavioural characteristics of Rett syndrome were similar across age groups and, where assessed, stable over time, as were repetitive behaviours generally and self-injury. There was some suggestion of deterioration in health arising with ageing, principally contributed to by deteriorations in dental and gastro-intestinal problems both with moderate effect sizes. Indicators of mood, interest and pleasure differed significantly across age groups. The total scale score significantly deteriorated over time, with a moderate effect size.

*Conclusions* This study provides further evidence for the post regression stability that characterises Rett syndrome. Emergent low mood in Rett syndrome requires further research.

## Introduction

Rett syndrome is a genetic disorder that causes severe cognitive and physical impairments. In its classic form, it appears to affect almost exclusively females, with an incidence of up to one in every 10 000 live female births. Its cause is most often a mutation in the methyl-CpG binding protein-2 (*MECP2*) gene, located on the X chromosome at *Xq28* (Amir *et al.* 1999). However, although a *MECP2* mutation is found in most cases of the classic form, Rett syndrome remains a clinical rather than a molecular diagnosis. *MECP2* mutations have not been found in all cases of Rett syndrome and mutation has been found in individuals who do not meet the clinical diagnostic criteria for classic or variant Rett syndrome (Hagberg 2002).

Neul *et al.* (2010) described revised diagnostic criteria for Rett syndrome. Classic Rett syndrome requires apparently normal psychomotor development in the first 6 months of life followed by a period of regression, which is not due to brain injury secondary to trauma, neurometabolic disease, or severe infection, and involves partial or complete loss of acquired purposeful hand skills and language, gait abnormalities and the development of stereotypic hand movements, followed by stabilization or even some degree of recovery. An important aspect of the regression is a period of social withdrawal or impaired communication. Atypical Rett syndrome requires a similar period of regression and subsequent stabilization/ recovery, at least two of the above four behavioural manifestations and the presence of at least five (out of 11) supportive criteria. Other variant forms have also been described (Neul *et al.* 2010).

As the above indicates, early development in Rett syndrome involves identifiable changes over time. Hagberg and Witt-Engerstrom (1986) devised a staging system that divides the natural history of Rett syndrome into four stages: early stagnation, rapid regression, stabilization and late motor deterioration. However, while survival into adulthood is not uncommon for individuals with Rett syndrome, there is a greater representation of children than adults in existing surveys tracking abilities and characteristic behaviour after stabilization. There is a need for further research on the behavioural characteristics of adults and on developmental trajectory into adulthood. Matson *et al.* (2008) assessed a small sample of adults with Rett syndrome using a number of standardized measures and compared them to groups with autism and intellectual disability and intellectual disability only. However, this did not provide a profile of possible age-related change.

Halbach *et al.* (2008) explored possible age-related change among a sample of 53 adolescents and adults with Rett syndrome, divided into three age groups: 16–19 years, 20–29 years and 30+ years. They reported no statistically significant differences in relation to general health, body mass index, respiratory problems other than apnea, musculoskeletal problems other than kyphosis, epilepsy, sleep problems and behavioural problems. Statistically significant differences were found in relation to communication skills, trophic skin and nail changes, apnea and kyphosis, which were all greater with increasing age. Halbach *et al.* (2013) followed up 37 individuals in this sample to explore age-related change longitudinally. They concluded that the situation over time was more or less stable, with a slow on-going deterioration of gross motor

functioning in contrast to better preserved cognitive functioning and reasonable general health.

The purpose here was to add to the evidence about age-related clinical and behavioural change into adulthood. Data on a variety of relevant clinical and behavioural measures from a UK national sample of people with Rett syndrome across the age range were analysed cross-sectionally to identify possible effects of ageing. In addition, a longitudinal follow-up was undertaken to explore change over time. The clinical characteristics, current abilities and health of the original sample are described in Cianfaglione *et al.* (2015 a) and their behavioural characteristics in Cianfaglione *et al.* (2015 b).

**Method**

Survey sample

Before commencing the study, ethical approval was granted by the Research Ethics Committee for Wales (Application number: 09/MRE09/50).

The survey methodology is described in greater detail in Cianfaglione *et al.* (2015 a). In brief, families were recruited through the British Isle Rett Syndrome Survey (BIRSS), an on-going database now maintained by Professor Angus Clarke at Cardiff University. 308 families with a daughter or son with Rett syndrome were approached and 126 (40.9%) returned a consent form. Questionnaire packs were then distributed and families were contacted first by telephone and then by letter if they had not returned the questionnaires within two months from receiving them. Ninety-three families returned completed questionnaires (30.2% of the original 308, 73.8% of those who consented to take part). Ninety-two participants with Rett syndrome were female and one was

male. The male participant was excluded from the final sample. One participant passed away during the study and was not included in the analysis.

The majority of participants in the initial sample were invited to take part in the follow up survey. A small number of families had returned initial questionnaires late and their inclusion would have reduced the follow-up period, which already was less than ideal. Questionnaires were distributed over a six-month period 16 months after the return of the initial survey questionnaire. A total of 72 questionnaires were distributed to families. Fifty families (69.4%) returned a second completed questionnaire.

Sample characteristics

The achieved sample comprised 91 girls and women with a diagnosis of Rett syndrome, of whom 80 (87.9%) lived at home and 11 (12.1%) lived in out of family placements. The sample was skewed towards people living in the family home as another research aim was to investigate the well-being of parents caring for a child with Rett syndrome (although this survey sought to include only individuals living with their parents, the information on the BIRSS database was not entirely up-to-date and a minority no longer did so). Ages ranged from 4 to 47 years with a mean of 20.5 years: 43 participants were children and 48 adults. Sixty-nine had classic Rett syndrome (75.8%), 19 atypical Rett syndrome (20.9%) and 3 another *MECP2*-related disorder (4.3%). Seventy-one were known to be *MECP2* positive (78.0%): 52 in the classic group and 16 in the atypical group in addition to the three with other *MECP2*-related disorder. Diagnosis of Rett syndrome was made by a paediatrician in 42.9% of cases, a clinical geneticist in 26.4%, by both a paediatrician and clinical geneticist in 3.3% and by another professional in 25.3% (this information was missing for the

remaining 2.2%). Median age of diagnosis was 3.0 years (range, 1-39 years). Diagnosis occurred most commonly between two and four years of age.

Regression was reported in 87 (95.6%). In one case (1.1%), the mother was not sure if the child had had a regression and, in 3 others (3.3%), all with *MECP2*-related disorder, they reported that the child did not have a regression. Mean age of regression was 18.9 months (range, 6-84 months; SD 11.75): 15 (16.5%) had a regression before 12 months, 49 (53.8%) between 12 and 18 months, 18 (19.0%) between 19 and 36 months and 5 (5.5%) after 36 months (including, one participant who had a late regression at 7 years).

The age of the follow-up sample ranged from 7 years to 48 years with a mean of 22.9 years: 20 participants were children and 30 adults.. Seventy-six percent of the sample was diagnosed with classic Rett syndrome, the remainder with atypical (20.0%) and *MECP2*-related disorder (4.0%). The majority (84%) had a confirmed mutation in the *MECP2* gene. The other 16.0% had either not been tested (10.0%) or the mutation was not known (6.0%). Age of regression was between 7 and 48 months, with a mean age of 18 months.

Measurement

Families were asked to complete two questionnaire packs. One questionnaire pack related to the person with Rett syndrome, covering their early development, current skills, health and behavioural characteristics. The second questionnaire pack related to various aspects of family experience. It is the first set of measures that are of concern here. After parents returned the completed questionnaire packs, the Vineland Adaptive Behavior Scale – Survey Form (Sparrow *et al.* 1984 - see below) was carried out as a telephone interview with one of the parents.

*Vineland Adaptive Behavior Scale – Survey Form* (VABS, Sparrow *et al.* 1984). The VABS Survey Form is a well established scale to assess adaptive behaviour in people with and without intellectual disabilities. It contains 297 items. The scale is divided into four domains: Communication, Daily Living, Socialization and Motor Skills. Standard scores (mean = 100; SD= 15) and age equivalent scores can be combined to derive an Adaptive Behavior Composite. Internal consistency (median Communication 0.89, Daily Living Skills 0.90, Socialization 0.86, Motor Skills 0.83, Adaptive Behavior Composite 0.94), test re-test reliability (Communication 0.86, Daily Living Skills 0.85, Socialization 0.81, Motor Skills 0.81, Adaptive Behavior Composite 0.88) and inter rater reliability (Communication 0.75, Daily Living Skills 0.72, Socialization 0.62, Motor Skills 0.78, Adaptive Behavior Composite 0.74) have been reported (Sparrow et al., 1984).

As participant scores were initially very low on this measure and the length of follow-up was short, it was not deemed suitable to administer the assessment again at follow-up.

*Rett Syndrome Behavioural Questionnaire* (RSBQ, Mount *et al.* 2002). The RSBQ is a 45-item checklist developed to assess behavioural and emotional characteristics of Rett syndrome. Items are rated 0 to 2, where 0 indicates that the behaviour is not true, 1 sometimes true and 2 often true. The scale is divided into eight subscales: General Mood, Breathing Abnormalities, Hand Behaviours, Repetitive Face Movements, Body Rocking and Expressionless Face, Night-time Behaviour, Fear/Anxiety, and Walking/Standing. High internal consistency has been reported for the total score (>0.90) and 8 subscales (0.60-0.79), with good

inter-rater and test-retest reliability scores (total score, >0.80; subscales, 0.60 - 0.79) (Mount *et al.* 2002).

*Health Questionnaire* (Hall *et al.* 2008). Information was requested about 15 possible medical problems in relation to two time periods: ever in their life and during the last month. Each problem is rated from 0=never to 3=severe. An Overall Health Score is obtained by summing the total for both time periods. Inter-rater reliability scores of 0.72 for health problems occurring in the person's life and 0.76 for the health problems occurring during the last month have been reported (Hall *et al.* 2008).

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

Immobile and non-verbal individuals are scored differently from those who can walk and/or speak. Scores on the Impulsivity subscale for non-mobile individuals are pro-rated to compare with those for mobile individuals. Good internal consistency, item level inter-rater reliability score ranges of 0.31-0.75

(mean 0.56) and test re-test reliability score ranges of 0.60-0.90 (mean 0.75) have been reported across the subscales (Burbidge *et al.* 2010).

*Mood, Interest and Pleasure Questionnaire Short-Form* (MIPQ-S, Ross & Oliver 2003). The MIPQ-S assesses mood, interest and pleasure levels in individuals with severe and profound intellectual disability. It contains 12 items scored using a 5-point Likert scale based on the respondents' observation of the participant in the last two weeks. High scores indicate positive mood and high interest and pleasure. There are two subscales: Mood, and Interest and Pleasure. Scores up to and including 15 and 6 (≤ 18 years) and 13 and 6 (>18 years) have been identified as being abnormally low and scores equal to or above 24 and 23 (≤ 18 years) and 24 and 21 (<18 years) as being abnormally high for the two subscales respectively (Ross *et al.* 2008). Inter-rater and test-retest reliability scores have been reported as good (0.85 and 0.97 respectively) as has internal consistency (Cronbach's alpha coefficient Total= 0.88, Mood= 0.79, Interest and Pleasure= 0.87) (Ross & Oliver 2003). Petry *et al.* (2010) found that a three factor model better fitted their MIPQ-S data, with subscales for Positive Mood, Negative Mood and Interest/pleasure.

*Repetitive Behaviour Questionnaire* (RBQ, Moss *et al.* 2009). The RBQ is a 19 item informant-based scale used to assess repetitive behaviour in individuals with intellectual disability. It has five subscales: Stereotyped Behaviour, Compulsive Behaviour, Restricted Preferences, Repetitive Use of Language, and Insistence on Sameness. However, the Repetitive Use of Language and Restricted Preferences subscales cannot be scored for individuals with no language as items require the person to be verbal. The frequency of behaviour on each item is scored on a 5-point Likert scale (0-4). Two scoring systems can be applied for

verbal (total score range, 0-76) and non-verbal individuals (total score range, 0-60). Items that are dependent on the person being verbal can be excluded when comparing verbal and non-verbal individuals. Clinical cut-offs for each subscale are reached if the individual scores three or more on at least 1 item (i.e., a behaviour occurs 'once a day' or 'more than once a day'). Inter-rater reliability scores ranging from 0.46 to 0.80 at item level and test-retest reliability scores ranging from 0.61 to 0.93 at item level have been reported (Moss *et al.* 2009). The following internal consistency coefficients have been reported (Moss *et al.* 2009): full-scale level >.80, the stereotyped behaviour and compulsive behaviour subscales both > .70, restricted preferences, repetitive speech and insistence on sameness subscales .50, .54 and .65, respectively.

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

Data analysis

For a few participants, some questionnaire items were missing even after attempting to complete them by contacting the respondents by telephone or using relevant information provided in response to another question. Guidelines from questionnaire manuals were employed for pro-rating missing data. Where the missing items were part of a scale or subscale, the mean for the scale/

subscale was substituted, providing that 75% of items were scored for the MIPQ and TAQ, 65% of items in each subscale were rated for the RBQ and 90% of items were rated for the RSBQ. Having done this, one case was excluded from the analysis of both the RSBQ and TAQ and two from the analysis of the MIPQ due to missing data. With regard to the follow-up data, similar conventions were followed and one case was excluded from the analysis of each of the MIPQ and RSBQ due to missing data.

Cross-sectional analysis: The Rett syndrome sample was divided into 4 age groups: <12 years (childhood: n=20, 22.0%), 12-17 years old (adolescence: n=23, 25.3%), 18-25 years (young adulthood: n=21, 23.1%) and 26+ years (adulthood: 27, 29.7%). Cross tabulation with associated chi-squared tests, non-parametric Mann-Whitney U tests or Kruskal-Wallis analysis of variance with post-hoc Mann-Whitney U tests together with non-parametric (Spearman) correlations were used to explore differences between groups and relationships between variables.

Longitudinal analysis: Wilcoxon rank-sum tests were used to analyse data longitudinally. Effect sizes were calculated where significant differences were revealed using the following formula: $r = z/\sqrt{N}$ where r is the estimated effect size, z is the z score and N the number of participants (Field 2009).

**Results**

Adaptive behaviour

There were significant differences between the age groups on the VABS Adaptive Behavior Composite and the Communication, Daily Living and Socialisation domain standard scores ($\chi^{2\,(3)} = 51.52, 42.52, 14.18, 75.97$; $p < .001, .001, .005$ .001 respectively), with in each case the childhood group (below 12 years) being

greater than the other three groups. However, there were no significant differences across age groups in raw scores or age equivalent scores, suggesting that adaptive behaviour was stable over time. Correlation of chronological age with VABS raw or age equivalent scores showed significant small positive associations between age and daily living skills raw scores ($r_s = .28$; $p < .05$), daily living skills age equivalent scores ($r_s = .29$; $p < .01$) and motor skills age equivalent scores ($r_s = .23$; $p < .05$).

Typical behavioural characteristics

There were no significant differences between age groups in the occurrence of hand stereotypies, teeth grinding, breath holding, hyperventilation, sleep difficulties, daytime sleepiness or Rett 'vacant episodes' (a behaviour often misidentified as a possible seizure in which the eye gaze is not fixed, the person appears not to be breathing, and there is an absence of hand movement or motor activity). There were also no significant differences between age groups on the RSBQ total or domain scores, a finding replicated when such scores were correlated with chronological age. There was no significant change in the RSBQ total or domain scores over time.

Health and mood

There were no significant differences between age groups with respect to scores on the Health Questionnaire, either in relation to the previous month or over the lifetime. However, there was an indication that health problems in the previous month were greater at follow-up than in the initial survey. Analysis indicated a significant increase in the total health score in relation to the previous month associated with a moderate effect size ($z = -2.983$, $p < .01$, $r = - 0.42$), principally

contributed to by deteriorations in dental problems (z = -2.707, p < .01, r = - 0.38) and gastro-intestinal problems (z = -2.322, p< .05, r = - 0.33).

All MIPQ-S scores other than the Negative Mood subscale significantly differed across age groups: Total score ($\chi^2$ (3) = 10.61; p< .05), Mood subscale score ($\chi^2$ (3) = 12.37; p< .01), Interest and Pleasure subscale score ($\chi^2$ (3) = 8.47; p< .05) and Positive Mood subscale score ($\chi^2$ (3) = 16.84; p< .01). Children below the age of 12 years had higher Total, Mood subscale, Interest and Pleasure subscale and Positive Mood subscale scores than the adolescent group, 12 – 17 years old (U =  on the MIPQ – S total score (U = 103.0, 109.0, 122.5, 94.5; z = -3.103, -2.972, -2.628, -3.315; p< .005, .005, .01, .005 respectively). In addition, children below the age of 12 had higher Mood subscale and Positive Mood subscale scores than the young adult group, 18-25 years old (U = 116.0, 92.5; z = -2.479, -3.102; p< .05, .005 respectively) and the adult group, 26+ years old (U = 123.5, 104.0; z = -3.054, -3.475 respectively; both p< .005). There were no significant differences between the adolescent and young adult groups or between the young adult and adult groups. However, the adolescent group had lower Total and Interest and Pleasure subscale scores than the adult group (U = 199.0, 173.5; z = -2.009, -2.529 respectively; both p< .05).

The MIPQ - S total score significantly deteriorated over time, with a moderate effect size (from 33.8 at Time 1 to 30.9 at Time 2, z= - 3.112, p< .005, r = - 0.44). However, changes in the subscale scores were non-significant. Analysed separately for each age group, total scores tended to be lower at follow-up for every age group. Change within the child (under 12 years at T1) and adolescent (12-17 years at T1) groups both just failed to reach significance (both p= .08). Change in the adult group (26+ years at T1) was significant, with a large effect

size (z= - 3.243, p< .05, r = - 0.62). As there were indications of deteriorating health in the previous three months and deteriorating mood between baseline and follow-up, change scores in each variable were correlated to explore whether these issues were associated. However, no significant correlation was found, either for the sample as a whole or for any age group.

Overactivity, impulsivity, repetitive behaviour and self-injury

The Activity Questionnaire total score differed across age groups ($\chi^2$ (3) = 11.46; p< .01), as did the Overactivity subscale score ($\chi^2$ (3) = 12.48; p< .01) and the Impulsivity subscale score for mobile participants ($\chi^2$ (3) = 9.55; p< .05). *Post-hoc* analysis revealed that children aged under 12 years had greater scores on all three aspects than the older three groups, which did not differ from each other. Chronological age was significantly inversely correlated with the Overactivity subscale score ($r_s$=-.24; p< .05) and the Impulsivity subscale score for mobile participants ($r_s$=-.31; p< .05). However, the total and subscale scores did not significantly change over time.

There were no differences across age groups on the Repetitive Behaviour Questionnaire, either in relation to the total score or the Stereotyped Behaviour, Compulsive Behaviour or Insistence on Sameness subscale scores. Nor were there differences in occurrence of self-injury (number of topographies) or severity of self-injury. All participants included in the longitudinal sample were reported to have repetitive hand stereotypies at both time points and 14 (28%) were reported to display self-injurious behaviour at both time points.

**Discussion**

In this paper, we presented data on the behaviour and health of 91 girls and women with Rett syndrome, analysed in four age categories, together with a

longitudinal follow-up of 50 participants. The sample was drawn from a national database and was reasonably large for a study of Rett syndrome. All families whose children met the criteria were invited to participate. In particular, both children and adults were represented, the latter being the slight majority. However, the sample was skewed towards those living in the family home as the main research purpose was to investigate the relationship between child characteristics and parental well-being. The 11 participants in out-of-family placements were, on average, older than those living in the family home (mean, 28.0 yrs vs. 19.5 yrs), albeit that the two groups were similar in age among the adults: almost all of the children lived with their parents. In addition, the two groups were similar in diagnostic distribution (82% classic vs. 75%), mean age of regression (18.5 months vs. 19.3) and mean severity score (9.0 vs. 8.5).

The response rate was low and it is not possible to assess the representativeness of the achieved sample. However, the age distribution was similar to a recent all-age, large sample (n=983) study of gastrointestinal and feeding problems (Motil *et al.* 2012). Moreover, over three-quarters of the sample had a positive mutation in the *MECP2* gene. Not all individuals in the sample had been tested, but in only one case diagnosed with classic Rett syndrome was a *MECP2* mutation not found. This is consistent with the literature that a mutation in the *MECP2* gene can be found in over 90% of cases with classic Rett syndrome (Neul *et al.* 2010). Consistent with other studies, the most common age of regression was between 12 and 18 months.

Cross-sectional analysis by age cannot give a definitive picture of age-related change as a number of factors confound the issue. First, one cannot assume that recent and past birth cohorts are necessarily equivalent. For example, survival of

more severely affected individuals or early developmental education may have improved over time. Second, differential mortality among more severely affected individuals may give rise to an 'healthy survivor' effect which might mask age-related decline. Hence, potential age-related change suggested by cross-sectional analysis should be confirmed by a longitudinal analysis. There was an attempt to do this in this study. However, the longitudinal follow-up was limited in two respects. First, practical considerations (i.e., length of funding) meant that the period of follow-up was short, only 16 months. Second, the sample size for the longitudinal analysis was smaller, albeit still slightly larger than the study cited in the introduction.

Adaptive behaviour was assessed only once. The cross-sectional analysis provided a picture of stability over time. The way of calculating standard scores resulted in the child group being different from the other three older groups. However, small positive associations were found between chronological age and daily living skills raw or age equivalent scores, suggesting that individuals may learn over time, albeit very slowly. There was also a small positive association between chronological age and motor skills age equivalent scores, which is inconsistent with the general understanding of late motor deterioration. However, as already indicated, the absence of deterioration in a cross-sectional analysis may be due to an healthy survivor effect.

There was also stability in behaviours characteristic of Rett syndrome, repetitive behaviour in general and in self-injury. The child group had significantly higher impulsivity and overactivity scores than the other three age groups but an ageing effect was not confirmed by longitudinal analysis. Possible

age-related change in these respects may be worthy of further research in view of the relatively short follow-up period examined here.

Halbach *et al.* (2013) concluded that general health was more or less stable over time. This study found no cross-sectional differences between age groups. However, the longitudinal element found declining health in certain respects over time. The absence of difference cross-sectionally may again be due to an healthy survivor effect. A longitudinal study of general health with a larger sample and longer follow-up period would seem to be merited.

The strongest indication of age-related deterioration found here was in relation to mood. The child group had more positive mood than the other three age groups and had higher interest and pleasure than the adolescent group, which did not differ from the young adult group. Moreover, there was significant deterioration over time in the total scale score, a deterioration which tended to be found for each age group, particularly among adults aged over 25 years. These results suggest that mood, interest and pleasure dip in adolescence and deteriorate with ageing. Although Berg *et al.* (2007) found in a cross-sectional analysis among individuals with severe or profound intellectual disabilities with three other genetic syndromes that health problems were related to low mood, we did not find an association here between increase in health problems and deterioration in mood. Emergent low mood in Rett syndrome and what might occasion deterioration over time requires further investigation.

In conclusion, this study provides further evidence that the post regression stability in the staging system proposed by Hagberg and Witt-Engerstrom (1986) does broadly characterise Rett syndrome with limited growth in adaptive behaviour and a characteristic behavioural pathology which remains similar

over time. However, there is some suggestion of deteriorating health which deserves further investigation. In addition, mood, interest and pleasure appear to decline as children become teenagers and this study provides reasonably convincing evidence of age-related deterioration, given its small sample size and short follow-up period. Such deterioration and the reasons underlying it need to be better understood.

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