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Comparing social reciprocity in preserved speech variant and typical Rett syndrome during the early years of life

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Abstract

This study compared early markers of social reciprocity in children with typical Rett syndrome (RTT) and in those with the preserved speech variant (PSV) of RTT. Retrospective video analysis of 10 toddlers with typical RTT and five with PSV investigated participants' orientation to their name being called between the ages of 5 and 24 months, prior to their diagnosis. From analysis of the recordings two distinct profiles were apparent. Although response rate was higher in girls with typical RTT than PSV at 5 to 8 months this noticeably reversed from 9 to 12 months onwards. By two years of age there was a markedly higher rate and range of responses from girls with PSV. This study contributes to the delineation of different profiles for the variants of RTT.

Keywords

Rett syndrome; preserved speech variant; family videos; home videos; response to name; retrospective video analysis; social awareness

1 Introduction

Rett syndrome (RTT) is a neurodevelopmental disorder of genetic origin, typically characterized by seemingly-normal development in the first year of life followed by a regression in and loss of skills. Individuals with RTT have previously been considered to be profoundly intellectually as well as communicatively impaired and to demonstrate autistic

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spectrum-like behaviors, in addition to displaying stereotyped hand movements and a loss in purposeful hand use (Cass et al., 2003; Didden et al., 2010; Downs et al., 2014; Hagberg, 2002; Hetzroni & Rubin, 2006; Neul et al., 2010; Percy, Gillberg, Hagberg, & Witt-Engerstrom, 1990; Quest, Byiers, Payen, & Symons, 2014; Smeets, Pelc, & Dan, 2012; Stasolla & Caffò, 2013; Trevarthen & Daniel, 2005). A number of variants of RTT have been identified which, following confirmation of a diagnosis of RTT through genetic analysis, can be distinguished from each other according to certain clinical criteria (Neul et al., 2010; Neul et al., 2014). In recent years, understanding more precisely the relationships between, and defining characteristics of, a genotype-phenotype match for both mutation type and variants of RTT has become an increasing focus for research (e.g., Kortum et al., 2011; Matson, Fodstad, & Boisjoli, 2008; Temudo et al., 2008; Temudo et al., 2011; Urbanowicz, Downs, Girdler, Ciccone, & Leonard, 2014a). In addition to classic or typical RTT, the milder 'Zappella' or preserved speech variant (PSV) (Renieri et al., 2009; Zappella, Mari, & Renieri, 2005) is one of the more studied variants, although the existing pool of knowledge regarding RTT, its variants and their characteristics pre- and post-diagnosis and pre- and post-regression is still relatively small.

A number of researchers have sought to fill the knowledge gap either by interviewing parents to elicit information about the early and current (pre- and post-regression) development of their child's communication skills (Urbanowicz, Leonard, Girdler, Ciccone, & Downs, 2014b) or by exploring the early (pre-diagnostic) development of children with RTT through the medium of retrospective video analysis. These retrospective studies have included both consideration of early general development (Burford, 2005; Einspieler, Kerr, & Prechtl, 2005; Einspieler et al., 2014) and socio-communicative / speech and language development in children with typical RTT (Bartl-Pokorny et al., 2013) and children with PSV (Marschik, Einspieler, Oberle, Laccone, & Prechtl, 2009; Marschik, Einspieler, Prechtl, Oberle, & Laccone, 2010; Marschik, Kaufmann, et al., 2012; Marschik, Pini et al., 2012; Marschik, Vollmann, et al., 2013). Other studies that we have conducted have also compared typical RTT and PSV (Marschik, Kaufmann, et al., 2013) and have drawn a comparison between typical RTT, PSV and a typically developing toddler (Marschik, Bartl-Pokorny, et al., 2013). What each of these studies has so far demonstrated is that the early development of children with RTT is not as asymptomatic as originally assumed and that deviations from typical development can be identified prior to the onset of regression.

One domain of socio-communicative development not explored in these retrospective analyses is that of social reciprocity in children with RTT. This area has been studied extensively, however, in relation to early identification of autism spectrum disorder (ASD) and other forms of developmental disability. Social reciprocity, or rather the lack of it, during the first two years of life has been demonstrated to be a significant indicator of a later diagnosis of ASD and/or developmental disorders (Baranek, 1999; Clifford, Young, & Williamson, 2007; Dawson, et al., 2004; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Osterling & Dawson, 1994; Osterling, Dawson, & Munson, 2002; Trevarthen & Daniel, 2005; Werner, Dawson, Osterling, & Dinno, 2000). In particular, observing the child's response to their name being called has been found to be a good marker of social reciprocity or social awareness. Studies have shown that infants as young as 4.5 to 5 months of age are able to demonstrate early signs of recognizing the sound pattern of their own

name, both through employing modified head-turn preference tests (Mandel, Jusczyk, & Pisoni, 1995) and through the use of near-infrared spectroscopy (Grossmann, Parise, & Friederici, 2010). These experiments do not suggest, however, that children of such a young age are yet able to imbue the name call with communicative intent, to recognize the ostensive signal. The ability to mentalize is thought not to develop until around 18 months of age (Frith & Frith, 2003). Indeed, different areas of the brain were triggered in the infants of 5 months old when responding to their name as opposed to adults reacting to their own name, in whom the area associated with mentalizing was found to be triggered (Kampe, Frith, & Frith, 2003). Nevertheless, at only 4.5 to 5 months old typically developing infants are at least able to recognize their own name as a personally-significant sound pattern and to react. The failure to respond to one's own name or to require more prompts before responding have both been found, through retrospective video analysis studies, to be significant and reliable early predictors of a later diagnosis of autism, and to distinguish autism from other forms of developmental delay and typically developing children between about 8 months to two years of age. Usually this is suggested to be in combination with other markers such as lack of eye contact rather than as a single factor (Baranek, 1999; Clifford, et al., 2007; Dawson, et al., 1998; Dawson, et al., 2004; Osterling & Dawson, 1994; Osterling, et al., 2002; Werner, et al., 2000). This same lack of response to name was also found to be significant by 12 months of age (though not at 6 months) in two prospective studies of infants at risk of ASD (Nadig et al., 2007; Zwaigenbaum et al., 2005).

The debate surrounding the similarities and differences between ASD and RTT and its variants has, in recent years, begun to be explored at two levels: one pertaining to the 'outer' observable, behavioral features of the conditions (the phenotypic representation) (Goldman & Temudo, 2012) and one relating to the 'inner' biological, genetic or epigenetic influences on brain structure and development (the genotypic representation) (Badcock & Crespi, 2006). Trevarthen and Daniel (2005) attempt to draw these two together. They liken the 'outer' behaviors witnessed during the regression stage of RTT to features of ASD, namely the reduction in interest in people accompanied by the apparently reduced communicative intent, difficulties in shared attention and changes in motor coordination. However, they go on to acknowledge that the renewed sociability and emotional sensitivity which emerge in the third stage of RTT set the two conditions apart, concluding that there is a different underlying 'inner' basis: "Notwithstanding that the two conditions show clear differences in both brain growth and early development of skills and sociability, the first signs of autism and Rett syndrome have important similarities" (S25, Abstract).

In the current study we focused on questions relating to early social awareness (social reciprocity) and RTT as a contribution to the growing body of knowledge and understanding about the characteristics of RTT and its variants, both before and during the regression phase. The aims of our descriptive study were three-fold:

- (a) To explore whether individuals with RTT demonstrate social awareness (social reciprocity) during the early years of life;
- (b) To determine whether there are changes over time which may span the pre- and post-regression period;

- (c) To ascertain whether there are significant differences in these social markers between typical RTT and PSV.

2 Method

Building on the methodological footsteps of many of the social reciprocity in autism studies as well as on our own previous work (Bartl-Pokorny, et al., 2013; Marschik, Bartl-Pokorny, et al., 2013; Marschik & Einspieler, 2011; Marschik, et al., 2009; Marschik, et al., 2010; Marschik, Kaufmann, et al., 2012; Marschik, Kaufmann, et al., 2013; Marschik, Pini, et al., 2012; Marschik, Vollmann, et al., 2013), we utilized retrospective video analysis as a way of observing behavioral responses to name as a marker of social reciprocity in girls with typical RTT and PSV between the ages of 5 and 24 months.

2.1 Participants

Fifteen girls with a confirmed genetic diagnosis of RTT were recruited for this study. All had uneventful pregnancy and birth histories, and were singleton births with birth weight, length, occipitofrontal circumference and Apgar scores all within normal limits. According to the genetic testing, the girls were all MECP2 positive. Ten girls met the clinical criteria for typical RTT and five met the criteria for PSV (Neul et al., 2010). Although the girls were of differing ages at the time of the study, retrospective video analysis focused on the participants when they were aged between 5 and 24 months of age, prior to diagnosis.

2.2 Ethical approval

The study was approved by the local research ethics committee and the parents gave informed consent to participation in the study and to the publication of the results.

2.3 Procedure

The procedure was similar to that reported in a previous study (Marschik, Bartl-Pokorny, et al., 2013) that compared the two variants of Rett syndrome. It also followed the retrospective video analysis procedures we previously employed to explore aspects of early socio-communicative development in both typical RTT (Bartl-Pokorny, et al., 2013) and PSV (Marschik, Kaufmann, et al., 2012). Video recordings had been made by parents during the course of typical daily activities as well as on special occasions (e.g. birthday parties), at a time when they had been unaware of their daughter's diagnosis of RTT. In total 2042 minutes of recorded footage was available for analysis across all participants. The videos were divided into four distinct age categories: 5 to 8 months (median 46 minutes), 9 to 12 months (median 77 minutes), 13 to 18 months (median 93 minutes), and 19 to 24 months (median 100 minutes). For the purposes of this study, the child's behavioral response to hearing her name being called was of interest as a marker of social reciprocity. Analysis and coding of behaviors was conducted by three members of the team (KDB, CE, PBM) with support from the Noldus Observer-XT tool. Where any disagreement arose between the coders (7% of behaviors), the sequences were discussed within the team and a consensus was agreed. Three categories of behavior (the dependent variables) were coded: "eyes and/or head", "eyes and/or head and verbal", "eyes and/or head and gestures". Definitions of these dependent variables are given in the key to Figure 2.

3 Results

Table 1 shows how often each participant's name was called and a response could be expected compared with how often they reacted during each time interval. It also illustrates how often no coding could be assigned due to there being no instances of the child's name being called during the video clips or no video being available for a particular child during a given time period. In all but two instances it can be seen that for all participants at all time intervals the number of responses actually observed was lower than the number expected. This appears to be irrespective of age or RTT variant. Further descriptive detail is illustrated in Table 2 and Figures 1 and 2.

Table 2 adds detail to show how the overall response rate for each of the two groups was calculated during each time interval whilst Figure 1 illustrates the changes in response rate over time more clearly as a comparison between the typical RTT and PSV groups.

Figure 2 illustrates graphically the modes of behavioral response(s) observed by group and time period.

The results indicate that the response rate was initially higher in girls with typical RTT than PSV, at 5 to 8 months, but that this was reversed from 9 to 12 months onwards. At 13 to 18 months there was a noticeably higher response rate from girls with PSV compared with typical RTT and this differential was maintained at two years of age with a markedly higher rate and range of responses from girls with PSV. The majority of responses involved eye contact and/or turning of the head, which remained at a reasonably consistent level throughout in the PSV group but dropped off in the typical RTT group. The girls with typical RTT used some vocalization to accompany their responses at a low level throughout although no accompanying gestures were observed in this group at any age. In contrast the girls with PSV only added accompanying vocalizations and gestures to their eye contact and/or turning of the head movements in the final time period, by age two years. Verbal behaviors and gestures were never observed together as a response to name in either group and, therefore, were not included as a coding option.

4 Discussion

The aims of our study – to explore whether individuals with RTT demonstrate social awareness during their early (pre-regression) years, whether there are changes that span the regression period, and whether there are different profiles for typical RTT and PSV, were grounded in the knowledge we have to date of the characteristics of RTT. One of the most prominent features of RTT is the four-stage pattern of stagnation and regression (Hagberg, 2002; Neul, et al., 2010), with stagnation in development beginning any time between 6 and 18 months of age in typical RTT and regression of acquired skills between the ages of one and four years. This period of regression has been noted to include a reduction in interest in people and objects even though eye contact may be maintained (Smeets, Pelc, & Dan, 2012). Following regression there is typically a so-called pseudo-stationary period during which there may be renewed interest in people and some development in communication skills (e.g., Trevarthen & Daniel, 2005), particularly through the use of eye gaze. PSV is

characterized by a milder presentation with, amongst other things, better verbal skills and a somewhat later onset of regression, reported to be from around two to four years of age (Marschik, et al., 2010; Renieri, et al., 2009; Zappella et al., 2005). The results of the current study could, therefore, be considered to be completely in line with these patterns as the response behaviors of the typical group peaked during the first period from 5-8 months and thereafter tailed off, indicating a stagnation then reduction in skill and/or interest. The PSV group's increased frequency of responses after the initial time block, with a peak at 18 months and relatively little tailing off by the age of two in comparison with the typical RTT group also concurs. The fact that the participants with PSV also demonstrated an increase in modalities at age two, which was not mirrored by the girls with typical RTT, may also be significant. However, without more in-depth qualitative analysis of the type of vocalizations and further observation beyond the age of two and into the post-regression/pseudo-stationary period, only tentative conclusions can be drawn, especially as the typical RTT group engaged in low level vocalizations throughout the period from 5 to 24 months. What is noticeable though is that gestures were absent, initially in both groups and throughout the entire observation period in the typical RTT group, perhaps serving as an early indication of the difficulties in purposeful hand use which later typify RTT (Downs et al., 2014). It is also clear that eye contact was the preferred mode of response, over gesture and vocalization, in both groups, a feature well documented in all variants of RTT (Smeets et al., 2012).

The debate about similarities and differences between RTT and autism continues with some authors identifying the putative similarities in genomic imprinting which underlie ASD and other syndromes including RTT (Badcock & Crespi, 2006), as well as the similarities of the (transient) autistic-like features that can be observed during the regression phase of RTT (Percy, 2011; Trevarthen & Daniel, 2005) or the persisting features of autism that can be observed, especially in milder forms such as PSV (Kaufmann, et al., 2012; Renieri, et al., 2009; Zappella, 1997). Other authors highlight the differences, for example in hand stereotypies, that can be observed when comparing the behaviors of individuals with RTT and ASD (Goldman & Temudo, 2012) and the greater social awareness exhibited by individuals with RTT (Djukic & McDermott, 2012; Kerr, Archer, Evans, & Gibbon, 2006) which serves to distinguish them from those with ASD. In a previous study (Marschik, Kaufmann, et al., 2012), we reported on the early presence of socio-communicative dysfunction in PSV, which may indeed be indicative of autistic features. We further suggested that these dysfunctions may persist beyond regression, but with age-specific profiles.

There are a number of interesting areas for future research related to the exploration of social reciprocity and the relationship between RTT and ASD. For example, it would be interesting to compare the profiles from the current study with profiles from studies into early social reciprocity in children later diagnosed with ASD. It is not possible to take the results from this study alone and draw any direct inferences in relation to either ASD or typically developing children as only children with RTT were studied. Further studies involving both a typically developing control group and a cohort of children with ASD are necessary for this. Additional profiling of the children with RTT according to both variant and mutation type would also add valuable information to the existing knowledge about genotype-phenotype relationships in RTT (Kortum et al., 2011; Matson et al., 2008; Temudo

et al., 2008; Temudo et al., 2011; Urbanowicz et al., 2014a). It may then be possible to delineate similarities and differences in social awareness between children with RTT, its variants, ASD and typical development.

The lack of a control group, or a comparator group such as a cohort with ASD, could be seen as a limitation of the study. So too can the general problems which beset retrospective video analysis (Marschik & Einspieler, 2011; Mosconi, Reznick, Mesibov, & Piven, 2009; Osterling, et al. 2002), for example, the contextual differences and lack of consistency between settings and situations, and the relatively short duration and gaps in availability of recordings for some participants. When taken together, these considerations do mean the findings must be interpreted with some caution.

However, in a field in which knowledge is limited, the study has served its stated aim of shedding further light on behaviors during the pre-regression phase of RTT and does respond to the need we previously identified to build a larger body of evidence to delineate different profiles for typical and atypical RTT (Marschik, Bartl-Pokorny, et al., 2013). It does seem possible to identify profiles of early social reciprocity (according to response to name), which may distinguish between typical RTT and PSV. When combined with the results of our previous studies, which examine other aspects of early socio-communicative, speech-language, movement and behavioral development (Bartl-Pokorny, et al., 2013; Einspieler, et al., 2005; Marschik, Bartl-Pokorny, et al., 2013; Marschik, et al., 2009; Marschik, et al., 2010; Marschik, Einspieler, & Sigafoos, 2012; Marschik, Kaufmann, et al., 2012; Marschik, Kaufmann, et al., 2013; Marschik, Lanator, Freilinger, Prechtl, & Einspieler, 2011; Marschik, et al., 2012), early developmental profiles of children with typical RTT and PSV may be delineated more comprehensively. Its contribution towards the building of composite profiles for the differing variants of RTT is the value of the current study.

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References

- Badcock C, Crespi B. Imbalanced genomic imprinting in brain development: an evolutionary basis for the aetiology of autism. *Journal of Evolutionary Biology*. 2006; 19(4):1007–1032. DOI: 10.1111/j.1420-9101.2006.01091.x [PubMed: 16780503]
- Baranek GT. Autism during infancy: a retrospective video analysis of sensory-motor and social behaviors at 9-12 months of age. *Journal of Autism and Developmental Disorders*. 1999; 29:213–224. [PubMed: 10425584]
- Bartl-Pokorny KD, Marschik PB, Sigafoos J, Tager-Flusberg H, Kaufmann WE, Grossmann T, Einspieler C. Early socio-communicative forms and functions in typical Rett syndrome. *Research in Developmental Disabilities*. 2013; 34:3133–3138.
- Burford B. Perturbations in the development of infants with Rett disorder and the implications for early diagnosis. *Brain & Development*. 2005; 27(Suppl 1):S3–S7. [PubMed: 16182489]
- Cass H, Reilly S, Owen L, Wisbeach A, Weekes L, Slonims V, et al. Charman T. Findings from a multidisciplinary clinical case series of females with Rett syndrome. *Developmental Medicine & Child Neurology*. 2003; 45:325–337. [PubMed: 12729147]

- Clifford S, Young R, Williamson P. Assessing the early characteristics of autistic disorder using video analysis. *Journal of Autism and Developmental Disorders*. 2007; 37:301–313. [PubMed: 17031450]
- Dawson G, Meltzoff AN, Osterling J, Rinaldi J, Brown E. Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders*. 1998; 28:479–485. [PubMed: 9932234]
- Dawson G, Toth K, Abbott R, Osterling J, Munson J, Estes A, Liaw J. Early social attention impairments in autism: social orienting, joint attention, and attention to distress. *Developmental Psychology*. 2004; 40:271–283. [PubMed: 14979766]
- Diden R, Korzilius H, Smeets E, Green VA, Lang R, Lancioni GE, Curfs LM. Communication in individuals with Rett syndrome: An assessment of forms and functions. *Journal of Developmental and Physical Disabilities*. 2010; 22(2):105–118. DOI: 10.1007/s10882-009-9168-2 [PubMed: 20339577]
- Djukic A, McDermott MV. Social preferences in Rett syndrome. *Pediatric Neurology*. 2012; 46:240–242. [PubMed: 22490770]
- Downs J, Parkinson S, Ranelli S, Leonard H, Diener P, Lotan M. Perspectives on hand function in girls and women with Rett syndrome. *Developmental Neurorehabilitation*. 2014; 17(3):210–217. DOI: 10.3109/17518423.2012.758183 [PubMed: 23869872]
- Einspieler C, Kerr AM, Prechtel HF. Is the early development of girls with Rett disorder really normal? *Pediatric Research*. 2005; 57:696–700. [PubMed: 15718369]
- Einspieler C, Marschik PB, Domingues W, Talisa VB, Bartl-Pokorny KD, Wolin T, Sigafos J. Monozygotic twins with Rett syndrome: Phenotyping the first two years of life. *Journal of Developmental and Physical Disabilities*. 2014; 26:171–182.
- Frith U, Frith CD. Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society of London. Series B, Biological sciences*. 2003; 358:459–473. [PubMed: 12689373]
- Goldman S, Temudo T. Hand stereotypies distinguish Rett syndrome from autism disorder. *Movement Disorders*. 2012; 27(8):1060–1062. DOI: 10.1002/mds.25057 [PubMed: 22711266]
- Grossmann T, Parise E, Friederici AD. The detection of communicative signals directed at the self in infant prefrontal cortex. *Frontiers in Human Neuroscience*. 2010; 4:201. [PubMed: 21088694]
- Hagberg B. Clinical manifestations and stages of Rett syndrome. *Mental Retardation and Developmental Disabilities Research Reviews*. 2002; 8:61–65. [PubMed: 12112728]
- Hetzroni OE, Rubin C. Identifying patterns of communicative behaviors in girls with rett syndrome. *AAC: Augmentative and Alternative Communication*. 2006; 22(1):48–61. DOI: 10.1080/17461390500387320 [PubMed: 17114158]
- Kampe KK, Frith CD, Frith U. "Hey John": signals conveying communicative intention toward the self activate brain regions associated with "mentalizing," regardless of modality. *Journal of Neuroscience*. 2003; 23:5258–5263. [PubMed: 12832550]
- Kaufmann WE, Tierney E, Rohde CA, Suarez-Pedraza MC, Clarke MA, Salorio CF, et al. Naidu S. Social impairments in Rett syndrome: characteristics and relationship with clinical severity. *Journal of Intellectual Disability Research*. 2012; 56:233–247. [PubMed: 21385260]
- Kerr AM, Archer HL, Evans JC, Gibbon F. People with mutation positive Rett disorder who converse. *Journal of Intellectual Disability Research*. 2006; 50:386–394. [PubMed: 16629931]
- Kortum F, Das S, Flindt M, Morris-Rosendahl DJ, Stefanova I, Goldstein A, et al. Dobyns WB. The core FOXP1 syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis. *Journal of Medical Genetics*. 2011; 48(6):396–406. DOI: 10.1136/jmg.2010.087528 [PubMed: 21441262]
- Mandel DR, Jusczyk PW, Pisoni DB. Infants' recognition of the sound patterns of their own names. *Psychological Science*. 1995; 6:314–317. [PubMed: 25152566]
- Marschik PB, Bartl-Pokorny KD, Tager-Flusberg H, Kaufmann WE, Pokorny F, Grossmann T, et al. Einspieler C. Three different profiles: Early socio-communicative capacities in typical Rett syndrome, the preserved speech variant and normal development. *Developmental Neurorehabilitation*. 2013; Early Online: 1-5. doi: 10.3109/17518423.2013.837537

- Marschik PB, Einspieler C. Methodological note: video analysis of the early development of Rett syndrome - one method for many disciplines. *Developmental Neurorehabilitation*. 2011; 14:355–357. [PubMed: 22136120]
- Marschik PB, Einspieler C, Oberle A, Laccone F, Prechtl HF. Case report: Retracing atypical development: a preserved speech variant of Rett syndrome. *Journal of Autism and Developmental Disorders*. 2009; 39:958–961. [PubMed: 19224352]
- Marschik PB, Einspieler C, Prechtl HF, Oberle A, Laccone F. Relabelling the preserved speech variant of Rett syndrome? *Developmental Medicine & Child Neurology*. 2010; 52:218. [PubMed: 20002131]
- Marschik PB, Einspieler C, Sigafoos J. Contributing to the early detection of Rett syndrome: the potential role of auditory Gestalt perception. *Research in Developmental Disabilities*. 2012; 33:461–466. [PubMed: 22119693]
- Marschik PB, Kaufmann WE, Einspieler C, Bartl-Pokorny KD, Wolin T, Pini G, et al. Sigafoos J. Profiling early socio-communicative development in five young girls with the preserved speech variant of Rett syndrome. *Research in Developmental Disabilities*. 2012; 33:1749–1756. [PubMed: 22699249]
- Marschik PB, Kaufmann WE, Sigafoos J, Wolin T, Zhang D, Bartl-Pokorny KD, et al. Johnston MV. Changing the perspective on early development of Rett syndrome. *Research in Developmental Disabilities*. 2013; 34:1236–1239. [PubMed: 23400005]
- Marschik PB, Lanator I, Freilinger M, Prechtl HF, Einspieler C. Early signs and later neurophysiological correlates of Rett syndrome. *Klinische Neurophysiologie*. 2011; 42:22–26.
- Marschik PB, Pini G, Bartl-Pokorny KD, Duckworth M, Gugatschka M, Vollmann R, et al. Einspieler C. Early speech-language development in females with Rett syndrome: Focusing on the preserved speech variant. *Developmental Medicine & Child Neurology*. 2012; 54:451–456. [PubMed: 22348320]
- Marschik PB, Vollmann R, Bartl-Pokorny KD, Green VA, van der Meer L, Wolin T, Einspieler C. Developmental profile of speech-language and communicative functions in an individual with the Preserved Speech Variant of Rett syndrome. *Developmental Neurorehabilitation*. 2013; 17:284–290. [PubMed: 23870013]
- Matson JL, Fodstad JC, Boisjoli JA. Nosology and diagnosis of Rett syndrome. *Research in Autism Spectrum Disorders*. 2008; 2:601–611.
- Mosconi MW, Steven Reznick J, Mesibov G, Piven J. The Social Orienting Continuum and Response Scale (SOC-RS): a dimensional measure for preschool-aged children. *Journal of Autism and Developmental Disorders*. 2009; 39:242–250. [PubMed: 18648919]
- Nadig AS, Ozonoff S, Young GS, Rozga A, Sigman M, Rogers SJ. A prospective study of response to name in infants at risk for autism. *Archives of Pediatrics & Adolescent Medicine*. 2007; 161:378–383. [PubMed: 17404135]
- Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al. Percy AK. Rett syndrome: revised diagnostic criteria and nomenclature. *Annals of Neurology*. 2010; 68:944–950. [PubMed: 21154482]
- Neul JL, Lane JB, Lee HS, Geerts S, Barrish JO, Annese F, et al. Percy AK. Developmental delay in Rett syndrome: data from the natural history study. *Journal of Neurodevelopmental Disorders*. 2014; 6:20. [PubMed: 25071871]
- Osterling J, Dawson G. Early recognition of children with autism: a study of first birthday home videotapes. *Journal of Autism and Developmental Disorders*. 1994; 24:247–257. [PubMed: 8050980]
- Osterling JA, Dawson G, Munson JA. Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation. *Development and Psychopathology*. 2002; 14:239–251. [PubMed: 12030690]
- Percy AK. Rett syndrome, exploring the autism link. *Archives of Neurology*. 2011; 68:985–989. [PubMed: 21825235]
- Percy A, Gillberg C, Hagberg B, Witt-Engerstrom I. Rett syndrome and the autistic disorders. *Neurologic Clinics*. 1990; 8:659–676. [PubMed: 2215462]

- Quest KM, Byiers BJ, Payen A, Symons FJ. Rett syndrome: a preliminary analysis of stereotypy, stress, and negative affect. *Research in Developmental Disabilities*. 2014; 35(5):1191–1197. DOI: 10.1016/j.ridd.2014.01.011 [PubMed: 24582142]
- Renieri A, Mari F, Mencarelli MA, Scala E, Ariani F, Longo I, et al. Zappella M. Diagnostic criteria for the Zappella variant of Rett syndrome (the preserved speech variant). *Brain & Development*. 2009; 31:208–216. [PubMed: 18562141]
- Smeets EE, Pelc K, Dan B. Rett Syndrome. *Molecular Syndromology*. 2012; 2:113–127. doi: 000337637. [PubMed: 22670134]
- Stasolla F, Caffò AO. Promoting adaptive behaviors by two girls with Rett syndrome through a microswitch-based program. *Research in Autism Spectrum Disorders*. 2013; 7(10):1265–1272.
- Temudo T, Ramos E, Dias K, Barbot C, Vieira JP, Moreira A, et al. Maciel P. Movement disorders in Rett syndrome: an analysis of 60 patients with detected MECP2 mutation and correlation with mutation type. *Movement Disorders*. 2008; 23(10):1384–1390. DOI: 10.1002/mds.22115 [PubMed: 18512755]
- Temudo T, Santos M, Ramos E, Dias K, Vieira JP, Moreira A, et al. Maciel P. Rett syndrome with and without detected MECP2 mutations: an attempt to redefine phenotypes. *Brain & Development*. 2011; 33(1):69–76. DOI: 10.1016/j.braindev.2010.01.004 [PubMed: 20116947]
- Trevarthen C, Daniel S. Disorganized rhythm and synchrony: early signs of autism and Rett syndrome. *Brain & Development*. 2005; 27(Suppl 1):S25–S34. DOI: 10.1016/j.braindev.2005.03.016 [PubMed: 16182487]
- Urbanowicz A, Downs J, Girdler S, Ciccone N, Leonard H. Aspects of speech-language abilities are influenced by MECP2 mutation type in girls with Rett syndrome. *American Journal of Medical Genetics Part A*. 2014a; doi: 10.1002/ajmg.a.36871
- Urbanowicz A, Leonard H, Girdler S, Ciccone N, Downs J. Parental perspectives on the communication abilities of their daughters with Rett syndrome. *Developmental Neuropsychology*. 2014b; Early Online: 1–9. doi: 10.3109/17518423.2013.879940
- Werner E, Dawson G, Osterling J, Dinno N. Brief report: Recognition of autism spectrum disorder before one year of age: a retrospective study based on home videotapes. *Journal of Autism and Developmental Disorders*. 2000; 30:157–162. [PubMed: 10832780]
- Zappella M. The preserved speech variant of the Rett complex: A report of 8 cases. *European Child & Adolescent Psychiatry*. 1997; 6:23–25. [PubMed: 9452915]
- Zappella M, Mari F, Renieri A. Should a syndrome be called by its correct name? The example of the preserved speech variant of Rett syndrome. *European Journal of Pediatrics*. 2005; 164:710. author reply 711–712. [PubMed: 16010564]
- Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioral manifestations of autism in the first year of life. *International Journal of Developmental Neuroscience*. 2005; 23:143–152. [PubMed: 15749241]

Figure 1. Changes in response rates of girls later diagnosed with typical Rett syndrome and the preserved speech variant to their name being called (reaction observed as a percentage of reaction expected), between 5 and 24 months of age.

Figure 2. A comparison between the behavioral responses of girls later diagnosed with typical Rett syndrome and the preserved speech variant to their name being called, between the ages of 5 and 24 months.

Eyes and/or head = the girl looks to the person who calls her name, i.e. she turns her head towards the person and/or moves her eyes to make eye contact with that person; eye contact is not accompanied by verbal behaviors or gestures. A positive coding may also include looking to the camera if the person holding the camera calls the child's name.

Eyes and/or head and verbal = any verbal behavior (e.g. (proto)word, unspecified vocalization) in addition to making eye contact.

Eyes and/or head and gestures = any gesture (e.g. waving to greet) in addition to making eye contact.

Table 1

A comparison of the expected versus observed reactions to name being called, in girls with preserved speech variant and typical Rett syndrome between the ages of 5 and 24 months.

Child	5-8 months		9-12 months		13-18 months		19-24 months	
	Reaction expected	Reaction observed	Reaction expected	Reaction observed	Reaction expected	Reaction observed	Reaction expected	Reaction observed
RTT 1	0	0	0	0	1	1	n/v	n/v
RTT 2	6	3	0	0	n/v	n/v	1	0
RTT 3	12	3	n/v	n/v	n/v	n/v	n/v	n/v
RTT 4	5	2	4	0	n/v	n/v	n/v	n/v
RTT 5	11	5	4	1	26	8	20	2
RTT 6	4	1	0	0	n/v	n/v	1	0
RTT 7	3	2	4	4	n/v	n/v	n/v	n/v
RTT 8	1	0	15	5	8	0	5	0
RTT 9	n/v	n/v	1	0	12	1	1	0
RTT 10	n/v	n/v	11	0	10	0	4	2
PSV 1	5	2	15	5	9	4	15	6
PSV 2	32	8	28	10	7	3	n/v	n/v
PSV 3	n/v	n/v	n/v	n/v	5	1	6	5
PSV 4	n/v	n/v	0	0	3	1	3	0
PSV 5	n/v	n/v	n/v	n/v	7	6	24	9

Reaction expected = occasions when participant's name was called and a response could be expected.

Reaction observed = participant's response according to defined behaviors.

n/v = no video available.

Table 2

Comparative data collection from retrospective video analysis of the responses to name being called in girls with preserved speech variant and typical Rett syndrome between 5 and 24 months of age.

Age (months)	Number of cases		Number of calls		Reaction not possible		Reaction expected		Reaction observed		No reaction		Response rate (%)		Total recording time (min)	
	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV	RTT	PSV
5-8	8	2	57	40	15	3	42	37	16	10	26	27	38.10	27.03	356	46
9-12	9	3	51	53	12	10	39	43	10	15	29	28	25.64	34.88	512	77
13-18	5	5	67	33	10	2	57	31	10	15	47	16	17.54	48.39	590	93
19-24	6	4	37	52	5	4	32	48	4	20	28	28	12.50	42.55	268	100

Number of cases = number of participants for whom video recordings were available during the defined age period, out of the total number of 15 participants.

Number of calls = total number of times that the collective participants' names were called in the video recordings for the defined age period.

Reaction not possible = total number of times that the collective participants' responses to their names being called could not be included, for example, when they were already looking at the person who called their name.

Reaction observed = total number of times that the collective participants responded according to one of the defined behaviors.

Reaction expected = total number of times that the collective participants' names were called minus the times that a reaction was not possible.

No reaction = total number of times that a reaction was expected but no behavioral response was observed.

Response rate = percentage of reactions observed in relation to reactions expected.