Research in Developmental Disabilities 33 (2012) 1749–1756

Contents lists available at SciVerse ScienceDirect

Research in Developmental Disabilities

Profiling early socio-communicative development in five young girls with the preserved speech variant of Rett syndrome

Peter B. Marschik [a,c], Walter E. Kaufmann [b,c], Christa Einspieler [a,*], Katrin D. Bartl-Pokorny [a], Thomas Wolin [a], Giorgio Pini [d], Dejan B. Budimirovic [c], Michele Zappella [d], Jeff Sigafoos [e]

[a] Institute of Physiology (Developmental Physiology and Developmental Neuroscience; IN:spired), Center for Physiological Medicine, Medical University of Graz, Austria
[b] Children's Hospital Boston, Harvard Medical School, Boston, MA, USA
[c] Center for Genetic Disorders of Cognition and Behavior, Fragile X Clinic, Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[d] Tuscany Rett Centre Versilia Hospital, Lido di Camaiore, Italy
[e] Victoria University of Wellington, New Zealand

ARTICLE INFO

Article history:
Received 17 April 2012
Accepted 18 April 2012
Available online 13 June 2012

Keywords:
Communicative forms and functions
Preserved speech
Speech-language development
Rett syndrome
Video analysis

ABSTRACT

Rett syndrome (RTT) is a developmental disorder characterized by regression of purposeful hand skills and spoken language, although some affected children retain some ability to speech. We assessed the communicative abilities of five young girls, who were later diagnosed with the preserved speech variant of RTT, during the pre-regression period (aged 12–24 months). Videotapes, obtained by parents during routine family situations and celebrations, were analyzed to identify communicative forms and functions used by these toddlers. Non-verbal communicative forms dominated over verbal-communicative forms for six of the eight identified communication functions. Although the girls used various non-verbal forms to make requests, for example, none of the individuals were observed to make choices or request information. Early peculiarities in the speech-language domain during the first year of life became more prominent and evident during the second year of life as general differences between typical development and atypical development become more obvious in RTT. These findings highlight the importance of assessing socio-communicative forms and functions at early age in children with RTT. The results suggest that speech-language functions did not appear to play a major role in the children's communicative attempts. We conclude that, even among children with the preserved speech variant, socio-communicative deficits are present before regression and persist after this period.

1. Introduction

Rett syndrome (RTT) is a neurodevelopmental disorder associated with profound intellectual disability, severe communication impairment, autistic-like behavior, and stereotyped hand movements coinciding with difficulties in purposeful hand use (Carter et al., 2010; Cass et al., 2003; Hagberg, Aicardi, Dias, & Ramos, 1983; Kerr, Archer, Evans, & Gibbon, 2006; Matson, Fodstad, & Boisjoli, 2008; Neul et al., 2010). Since the identification of mutations in the X-linked

* Corresponding author at: Institute of Physiology, Center for Physiological Medicine, Medical University of Graz, Harrachgasse 21/5, 8010 Graz, Austria. Tel.: +43 316 380 4266; fax: +43 316 380 9630.
E-mail address: christa.einspieler@medunigraz.at (C. Einspieler).

0891-4222 © 2012 Elsevier Ltd. Open access under CC BY-NC-ND license.
http://dx.doi.org/10.1016/j.ridd.2012.04.012

MECP2 gene as the main etiology of RTT (Amir et al., 1999), the phenotypical features and neurobiological mechanisms underlying RTT have become increasingly better understood. Clinical phenotypes and diagnostic criteria were recently refined for classic RTT as well as for the three main variant forms: the early seizure variant (Hanefeld Variant), the congenital variant (Rolando Variant), and the preserved speech variant (PSV, Zappella Variant; Neul et al., 2010). A requirement for the diagnosis of classic RTT and its variants is the presence of a period of regression followed by recovery or stabilization. In classic RTT, these two periods are part of a four-stage course. First, the early period with subtle signs of abnormality is followed by a stage of marked and progressive deterioration that leads to dramatic loss of the ability in adaptive functioning, functional hand use, mobility, language and communicative functions. Following this regression, characteristic hand stereotypies become more prominent and cardinal features like breathing irregularities, seizures, autistic-like behavior, social impairments, unsteady gait, apraxia, and intellectual disability become more evident. During the late deterioration stage reduced mobility, dystonia and scoliosis are some of the prominent features (Cass et al., 2003; Charman et al., 2002; Hagberg et al., 1983; Kerr, 2001; Neul et al., 2010; Percy et al., 2010; Rajaei et al., 2011).

Focusing on the pre-regression period of RTT, our studies have so far contributed to the delineation of early abnormalities in both developing motor behaviors and early verbal behaviors (Einspieler, Kerr, & Prechtl, 2005a, 2005b; Marschik, Einspieler, Oberle, Laccone, & Prechtl, 2009; Marschik, Einspieler, Prechtl, Oberle, & Laccone, 2010; Marschik, Einspieler, & Sigafoos, 2012; Marschik, Lanator, Freilinger, Prechtl, & Einspieler, 2011; Marschik, Pini, et al., 2012). Of special interest is the analysis of early vocalizations in females with PSV, a mild variant of RTT associated with relatively better speech-language abilities. In previous studies of this variant, we observed an intermittent mix of typical and atypical vocalizations from the first months of life onwards. One of the most salient features was an abnormal inspiratory type of vocalization i.e., proto-vowel or proto-consonant alternations produced on ingressive airstream and breathy voice characteristics (Marschik, Pini, et al., 2012). This atypical quality of vocalization was evident to professionals and to naive listeners, thus suggesting that auditory Gestalt perception is a potential contributor for the detection of early deviations in females with RTT (Marschik, Einspieler, et al., 2012).

An extension to these findings and of high relevance to the understanding of speech-language and communicative development, is the study of pre-regressional pragmatic functions and socio-communicative capacities in RTT (e.g., request for an object, comment, choice making, imitation). It has been reported that individuals with RTT use various idiosyncratic behaviors (e.g., eye gaze, non-conventional vocalizations, facial expressions, or body movements) for communicative purposes (Dahlgren Sandberg, Ehlers, Hagberg, & Gillberg, 2000; Sigafoos et al., 2011; Sigafoos, Woodyatt, Keen, et al., 2000; Sigafoos, Woodyatt, Tucker, Roberts-Pennell, & Pittendreigh, 2000). An efficient tool to accurately document these potential communicative forms and functions of children with severe communication impairment, which has also been applied to individuals with RTT during their later stages of development, is the Inventory of Potential Communicative Acts (IPCA; Didden et al., 2010; Sigafoos, Arthur-Kelly, & Butterfield, 2006; Sigafoos, Woodyatt, Keen, et al., 2000; Sigafoos, Woodyatt, Tucker, et al., 2000). However, to the best of our knowledge, the IPCA has not yet been used to document pre-regressional socio-communicative capacities of children with the PSV of RTT. As pre-regressional behavior might be a precursor to post-regressional communicative functions in RTT, we evaluated the development of potential communicative functions of conventional and/or unconventional character during the second year of life of five young girls with PSV. This study addressed the following questions: (a) What, if any, potential communicative acts can be observed during the second year of life in young girls with the PSV of RTT? (b) What pragmatic functions are represented in the girls' communicative acts repertoires? (c) Do young girls with PSV use non-verbal communicative forms more frequently than verbal communicative forms? And (d) How complex is the gestural repertoire during this age period in PSV?

2. Methods

2.1. Participants

Participants were five young girls with PSV who were longitudinally observed from 12 to 24 months of age, before the onset of any RTT associated regression. Four of them came from Italian-speaking families and one participant was German (Case 5). All females were singletons, born as a result of uneventful pregnancies and deliveries. The mean birthweight was 3048 g (SD = 216 g) and birth lengths, occipitofrontal circumferences, and Apgar scores were in the normal range. Genetic testing revealed the following *MECP2* mutations: C468G in one, c.1163del44 in one, R133C in two, and a large intragenic deletion (c.378–43_964delinsGA) in one participant. The motor development of Case 5 and the vocalizations during infancy for all participants were described in Marschik et al. (2009) and Marschik, Pini, et al. (2012). All participants met the clinical criteria for PSV (Neul et al., 2010; Renieri et al., 2009). The study was approved by the local research ethics committees. Parents gave their informed consent to this longitudinal research and to the publication of the results.

2.2. Procedure

The data for this study was extracted from video footage made during typical family routines (e.g., play situations, bathing, feeding, etc.) and special events (e.g., Christmas or birthdays). All videos had been made by the parents, who were not aware at that time that their daughters had RTT. The footage of all five participants comprised a total of 224 min recorded in 223 clips (medians: 33 min; 26 clips). A research assistant naive to the purpose of the study checked the recordings for

sufficient length and quality standards, copied the relevant video recordings and prepared them for analysis (unifying the codecs and sampling the recordings across the age range).

The retrospective video footage was analyzed in order to document the occurrence of age-specific potential communicative acts, such as vocalizations, body movements, facial movements, eye gazing, gestures, onomatopoetics, and (proto)words as described by Sigafoos et al. (2006) and Sigafoos, Woodyatt, Keen, et al. (2000). All vocalizations, verbal utterances, gestures, and other communicative behaviors were transcribed in chronological order. Each transcript and coding (by PBM) was rechecked by a second transcriber (KDB) against the audio–video files to ensure accuracy and consistency. In case of disagreement, the video sequences in question were discussed within the team (PBM, KDB, CE) until agreement was achieved. The final transcriptions formed the basis for the analyses of the video data, which were based on the following inventories: the Austrian-German adaptations of the MacArthur–Bates Communicative Development Inventories, a checklist to assess early socio-communicative functions, early gestures, vocabulary, and grammar (ACDI; Marschik, Einspieler, Garzarolli, & Prechtl, 2007); and the Inventory of Potential Communicative Acts (IPCA), an inventory to define individual behaviors used for communicative purposes in 10 different communicative functions (i.e., social convention, attention to self, rejection/protestation, request for an object, request for an action, request for information, comment, choice making, answer, imitation; Sigafoos et al., 2006; Sigafoos, Woodyatt, Keen, et al., 2000). The analysis was partly carried out by means of the Noldus Observer-XT device. The two independent raters (PBM, KDB) achieved a high interrater agreement in their observations (Cohen's kappa = 0.86). Considering that the focus of our analyses was a description of early communicative forms and functions we decided to provide a conjoint description for both the German and Italian individuals.

3. Results

3.1. Potential communicative acts during the second year of life

Table 1 lists the potential communicative acts observed during the analyzed video footage. Forms observed included body movements, facial expressions, eye movements, and vocalizations. Symbolic forms of reference (e.g., spoken words) were rarely observed. Overall, the data in Table 1 indicate that only a limited number of communicative forms were observed during the participants' second year of life.

3.2. Presumed pragmatic functions

The classification of the various behaviors listed in Table 1, in terms of presumed pragmatic function (Table 2), revealed that all five participants used at least one of their communicative forms to express a request for an object or to comment on something. However, none of the girls ever showed any actions that could be classified as requesting information or choice making (Table 2). Only two of the five girls (cases 4 and 5) showed communicative acts in the remaining eight communicative categories (social convention, attention to self, reject/protest, request object, request action, commenting, answering, imitating; Table 2).

3.3. Verbal and non-verbal communicative forms

Despite the fact that all of the girls had some speech-language skills, non-verbal communicative forms dominated over verbal (vocalizations and speech) across six of the eight pragmatic categories. For commenting and answering, however, non-verbal behaviors and verbal-behaviors were equally represented. For the pragmatic function of rejection, more

Table 1
Potential communicative acts during the second year of life in five females with PSV.

Body movements	Facial expression/eye movements	Vocalizations	Symbolic forms
Reaching	Eye contact	Unspecified vocalization	Gestures[a]
Clapping with hands	Joint attention	Fussing	Protowords
Patting	Gazes away	Crying	Single words
Raising arms	Smile	Pleasure vocalization	Word combinations
Extending arms		Laugh	
Touching (person)		Onomatopoetics	
Grabbing objects			
Hugging a person			
Showing a toy			
Passing a toy to other person			
Taking person by their hand			
Imitation of manual routine			
Moving closer			
Moving away			

Categories adapted from Sigafoos, Woodyatt, Keen, et al. (2000).

[a] Gestures are listed in this category although some of the gestures used are not of symbolic character, but rather deictic.

Table 2
Individual profiles of communicative acts during the second year of life in five females with PSV: presence (●) or absence (□) of specific behaviors in the respective IPCA-categories (Sigafoos et al., 2006; Sigafoos, Woodyatt, Keen, et al., 2000).

	MECP2 mutation	Social convention	Attention to self	Reject/ Protest	Request object	Request action	Request info	Comment	Choice making	Answer	Imitate
Case 1	R133C	●	●	●	●	●	□	●	□	●	□
Case 2	C468G	□	□	□	●	□	□	●	□	□	●
Case 3	R133C	●	□	□	●	□	□	●	□	●	□
Case 4	c.1163del44	●	●	●	●	●	□	●	□	●	●
Case 5	c.378-43_964delinsGA	●	●	●	●	●	□	●	□	●	●

Table 3
The non-verbal and verbal communicative acts during the second year of life in five females with PSV: numbers stand for the number of individuals showing specific communicative behaviors assignable to the respective IPCA categories (Sigafoos et al., 2006; Sigafoos, Woodyatt, Keen, et al., 2000).

	Social convention	Attention to self	Reject/ protest	Request object	Request action	Request info	Comment	Choice making	Answer	Imitate
Non-verbal behaviors	4	3	0	4	3	0	3	0	3	2
Non-linguistic-verbal-behaviors	1	1	2	3	0	0	3	0	1	1
Linguistic-verbal behaviors	1	1	1	1	2	0	3	0	3	0

Table 4
Gestural repertoire of five females with PSV during the second year of life.

	MECP2 mutation	Waving indicating bye bye	Index finger pointing	Extended arms seeking comfort	Shaking the head indicating no	Head nodding indicating yes	Sending kisses	Total number of gestures used
Case 1	R133C	●	□	●	□	□	□	2
Case 2	C468G	□	□	●	□	□	□	1
Case 3	R133C	●	□	●	□	□	□	2
Case 4	c.1163del44	□	●	●	●	●	□	4
Case 5	c.378-43_964delinsGA	●	●	●	●	□	●	5

● Presence and □ absence of gestures

individuals exhibited verbal communicative forms. Such forms were, however, still relatively rare and of limited complexity (mainly onomatopoetics or single words). None of the females showed verbal imitation behaviors (linguistic vocalizations; Table 3).

3.4. The gestural repertoire

The gestural repertoire was limited in all of the five females throughout the observation period. The composition of the gestural repertoire was between one to five different gestures per child (Table 4).

4. Discussion

Socio-communicative development during the pre-regression period in individuals with RTT and its variants, especially the PSV, is still not well understood. Most of our knowledge about early speech-language capacities in individuals with this neurodevelopmental disorder is based on notes in medical records, or retrospective parental questionnaires and interviews conducted after the RTT diagnosis is made. However, such methods have limitations when the aim is to describe early communicative forms and functions (e.g., long time lag between the first concerns of the family and formal diagnosis; lack of parental training for observing linguo-cognitive development; checklists are not designed for linguistic analyses; e.g. Fehr et al., 2011; Marschik et al., 2007). A method that leads to early developmental data, by focusing on the child's natural surroundings and circumventing confounding effects such as parental memory bias, is the retrospective analysis of family videotapes (Einspieler, Widder, Holzer, & Kenner, 1988; Luyster, Lopez, & Lord, 2007; Marschik & Einspieler, 2011). This video analysis method can lead to a detailed delineation of developing communicative functions and behavioral peculiarities before diagnosis and thus contributes to a better understanding of early development in RTT and other neurodevelopmental disorders (Maestro et al., 2001; Marschik & Einspieler, 2011; Ozonoff et al., 2011; Palomo, Belinchón, & Ozonoff, 2006; Saint-Georges et al., 2010).

The potential value of analysis of early vocalizations and other communicative forms to ascertain the integrity of the young nervous system on the one hand or, if delayed or abnormal in character, to indicate developmental disability on the

other has been previously noted (Esposito & Venuti, 2010; LaGasse, Neal, & Lester, 2005; Marschik, Einspieler, et al., 2012; Marschik, Pini, et al., 2012; Nathani, Oller, & Neal, 2007; Oller, Eilers, Neal, & Schwartz, 1999; Paul, Fuerst, Ramsay, Chawarska, & Klin, 2011). Given that early vocal behavior is considered to be a precursor and prerequisite for further speech-language and communicative acquisition, we intended to track down its developmental pathway during the second year of life since this is usually a period of intensive development and growing complexity of speech-language functions. In fact, early peculiarities in the speech-language domain during the first year of life (reported in Marschik et al., 2009, 2010; Marschik, Einspieler, et al., 2012; Marschik, Pini, et al., 2012) became more prominent and evident during the second year of life as general differences between typical development and atypical development become more obvious in RTT.

Similar to the communicative patterns that have been reported for individuals with RTT at later stages of development (Didden et al., 2010; Sigafoos et al., 2009; Sigafoos, Woodyatt, Tucker, et al., 2000), in this study we also observed various body movements, facial expressions, eye movements, vocalizations and – although rarely – even symbolic forms of representation (gestures, words and word combinations) as forms of communication during the second year of life (see Table 1). Nonetheless, the repertoire of all these communicative forms can be considered poor or restricted (see Tables 2–4). The quality of various observed communicative behaviors was also abnormal (e.g., repetitive character of movements or vocalizations – echolalia; delayed response when called; bizarre smiling as reported for females with classic RTT during the first year of life; Einspieler et al., 2005b). These findings reinforce the assumption made in one of the first papers on PSV by Zappella, Gillberg, and Ehlers (1998), that mild abnormalities in socio-communicative interaction are already present during the pre-regression period.

Because aberrant and/or idiosyncratic behaviors evidently differ from pre-linguistic forms of communication, which constitute precursors of linguistic forms of reference and communication in typical speech-language acquisition, they should perhaps be labeled and treated differently and more tentatively interpreted as forms of communication. Thus, when it comes to describing the socio-pragmatic functions of individuals with such extreme communicative restrictions, it may be best to refer to such behaviors as "potential communicative acts" (as suggested by Sigafoos, Woodyatt, Keen, et al., 2000) instead of non-symbolic or pre-linguistic forms of communication (Didden et al., 2010; Siegel-Causey & Guess, 1989; von Tetzchner et al., 1996).

In a study applying the IPCA to 120 individuals with RTT (aged between 5 and 55 years), Didden et al. (2010) reported that the participants used eye contact/eye gaze as the most common form of communication and that symbolic forms of communication were rarely observed. Didden et al.'s findings are consistent with those of another study by Cass et al. (2003). Lavas, Slotte, Jochym-Nygren, Van Doorn, and Witt-Engerstrom (2006), however, noted that more than one third of their participants used symbolic forms of communication, but this was accomplished through the use of augmentative communication aids, which have been notoriously difficult to teach to children with RTT (Sigafoos et al., 2009). In addition, Didden et al. (2010) questioned whether such symbolic forms were consistently used for communicative purposes. In line with these considerations, the participants in the present study were also observed to emit some potential communicative acts in what might be seen as non-communicative settings. Consequently, the potential communicative forms and functions observed in video samples must be interpreted with caution because it is not always clear whether a certain behavior is in fact a form of communication, as opposed to a mere orienting response to an environmental stimulus.

In the present sample of children with PSV, non-verbal communicative behaviors dominated over verbal forms of communication. Nonetheless, as in previous studies (Renieri et al., 2009; Zappella et al., 1998; Zappella, Meloni, Longo, Hayek, & Renieri, 2001), a certain amount of verbal communicative acts, although limited and of altered quality, could also be observed before the onset of regression. Dividing verbal behaviors into non-linguistic and linguistic forms (Table 3) revealed that three participants used the latter for answering or commenting; for all other categories, the children rarely used conventional or proto-conventional forms of communication. Interestingly, we could not observe imitation behavior of linguistic forms. The only participant who verbally imitated her mother did so once by copying the prosodic structure of an exclamation. In addition, as reported earlier (Dahlgren Sandberg et al., 2000; Tams-Little & Holdgrafer, 1998), the gestural repertoire was very limited (Table 4) with a maximum of five different gestures (range 1–5). The same holds true for observed joint attention behaviors (Dahlgren Sandberg et al., 2000; von Tetzchner, 1997) that can be considered to play a central role in identifying gestures with communicative intent. We agree with Tams-Little and Holdgrafer (1998) in that a limited repertoire of gestures, in conjunction with a developmental delay and qualitative peculiarities in other speech-language domains, might be characteristic for a severe neurodevelopmental disorder like RTT.

The presence of some forms of verbal communicative function has been considered a feature of a mild RTT clinical presentation (Kerr et al., 2006). Mild forms have been associated with *MECP2* mutations such as R133C and C-terminal deletions (Bebbington et al., 2008; Kerr et al., 2006; Renieri et al., 2009), as it was the case for most subjects reported here. Nevertheless, we and others have also shown that relatively "milder" mutations like R133C are associated with greater prominence of autistic features (Kaufmann et al., 2012; Young et al., 2008; Zappella et al., 1998, 2001, 2003). Similar to the association of these and other "milder" mutations (e.g., R294X, R306C) with prominent behavioral problems such as anxiety and mood instability (Robertson et al., 2006), it is unclear whether easier identification of aberrant behaviors is the consequence of overall decreased neurologic impairment. Nonetheless, our findings of restricted socio-pragmatic functions (such as an impairment in joint attention and imitation), might represent early signs of autistic behavior and allow a new insight into its developmental pathway in RTT. Any conclusions are also tentative due to the well known limitations of retrospective video analysis (e.g., Marschik & Einspieler, 2011) and the small sample size of the present study. Further investigation on this topic is needed to delineate early peculiarities in the speech-language domain and to assess the general validity of these findings in RTT.

The IPCA is reported to be appropriate for gathering descriptive information with adequate inter-observer agreement and good predictive validity for identifying intervention targets; furthermore IPCA results are in agreement with naturalistic observations (Keen, Woodyatt, & Sigafoos, 2002; Sigafoos, Woodyatt, Keen, et al., 2000; Sigafoos, Woodyatt, Tucker, et al., 2000; Tait, Sigafoos, Woodyatt, O'Reilly, & Lancioni, 2004). The IPCA was originally intended for use as an interview protocol with parent, teacher, or caregiver informants (Sigafoos et al., 2006; Sigafoos, Woodyatt, Keen, et al., 2000; Sigafoos, Woodyatt, Tucker, et al., 2000). Our study is important in being the first to gather descriptive information on communicative behaviors in girls with PSV, applying this tool for analyses of retrospective home videos. A great advantage of this assessment is that no inherent bias of indirect, third-party reports is reflected in the results. On the other hand, it is possible that these video segments did not provide sufficient sampling of the full range of communicative forms and functions in these children's repertoires (Fyfe et al., 2007; Marschik & Einspieler, 2011). For example, the fact that no child was observed to make choices, but that all of them were observed to request objects is very interesting given that requesting and choice making would seem to be similar ways of gaining access to preferred objects. This discrepancy could suggest that there were fewer opportunities for choice making, as compared to requesting, or that choice making is a very different (and perhaps more advanced) form of communication compared to requesting. A third possible explanation for this discrepancy is that perhaps requesting was far easier to observe in these video segments than was choice making. In any of these cases, the discrepancy points to possible limitations in the use of naturalistic video analysis versus the use of direct, structured protocols (where specific numbers and types of opportunities can be created) for assessing a child's communicative ability.

One of the main difficulties we faced in the analysis of these videos was related to our attempt to quantify gestures. The repertoire of the participants might be to some extent larger than reported here, but nonetheless the restricted repertoire and its qualitative deviations could be detected from the given dataset. Furthermore, some of the items on the 10 subscales of the IPCA did not seem to be applicable in their present form to 2-year-old children (e.g., the issue of clarification in the subscale requesting information). For future research on communicative functions in toddlers, modifications of the IPCA might facilitate analysis and avoid potential misinterpretations.

5. Conclusions

Our study, even though conducted with a small sample of individuals with a rare genetic disorder, demonstrates that the combination of IPCA with retrospective video analysis is a powerful tool for describing early communicative capabilities in developing children. It may be a source for delineating individual differences and atypical communicative parameters. Still, further research is needed to document the potential predictive power and relationships between early communication behavior and long-term communication skills. Nonetheless, this method seems to have great potential for the assessment of early socio-pragmatic functions and intervention planning for children with special needs.

In individuals with RTT and PSV, prominent autistic behavior has been described as associated feature (Kaufmann et al., 2012; Percy, 2011; Renieri et al., 2009; Zappella et al., 1998). Our findings highlight the early presence of socio-communicative dysfunction in PSV, perhaps a component of the autistic cluster reported in 76% of these individuals (Renieri et al., 2009). Considering that it has been recently reported that, in females with RTT, autistic features might persist after the regression period (Kaufmann et al., 2012; Matson, Dempsey, & Wilkins, 2008; Mount, Charman, Hastings, Reilly, & Cass, 2003; Wulffaert, Van Berckelaer-Onnes, Scholte, 2009; Zappella et al., 1998), these findings contribute to the notion that socio-communicative dysfunctions are not transient but rather persistent though with age-specific profiles in RTT.

Among others, we discussed that abnormal spontaneous vocalizations might point to severe developmental disabilities suggesting a closer follow up of individuals with an early abnormal vocal repertoire (LaGasse et al., 2005; Marschik, Einspieler, et al., 2012; Marschik, Pini, et al., 2012; Paul et al., 2011). The developmental trajectory of peculiar vocalizations, followed by profound delay and deviations in socio-communicative development, strengthens the claim that early verbal functions represent an essential and easily detectable parameter for determining the integrity of neural functions.

Acknowledgements

We would like to express our sincere gratitude to all parents for providing their audio–video data; further to all colleagues who helped to conduct the study, especially Ing. Gunter Vogrinec for technical assistance. The study was supported by the Austrian Science Fund (FWF; P19581-B02), Koerner Fond, Country of Styria; and the Lanyar Foundation (P325, P337); PBM supported by COST Action BM1004.

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.

Bebbington, A., Anderson, A., Ravine, D., Fyfe, S., Pineda, M., de Klerk, N., et al. (2008). Investigating genotype-phenotype relationships in Rett syndrome using an international data set. *Neurology, 70*, 868–875.

Carter, P., Downs, J., Bebbington, A., Williams, S., Jacoby, P., Kaufmann, W. E., et al. (2010). Stereotypical hand movements in 144 subjects with Rett syndrome from the population-based Australian database. *Movement Disorders, 25*, 282–288.

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

Charman, T., Cass, H., Owen, L., Wigram, T., Slonims, V., Weeks, L., et al. (2002). Regression in individuals with Rett syndrome. *Brain and Development, 24*, 281–283.

Dahlgren Sandberg, A., Ehlers, S., Hagberg, B., & Gillberg, C. (2000). The Rett syndrome complex: Communicative functions in relation to developmental level and autistic features. *Autism, 4*, 249–267.
Didden, R., Korzilius, H., Smeets, E., Green, V. A., Lang, R., Lancioni, G. E., et al. (2010). Communication in individuals with Rett syndrome: An assessment of forms and functions. *Journal of Developmental and Physical Disabilities, 22*, 105–118.
Einspieler, C., Kerr, A. M., & Prechtl, H. F. (2005a). Abnormal general movements in girls with Rett disorder: The first four months of life. *Brain and Development, 27*, 8–13.
Einspieler, C., Kerr, A. M., & Prechtl, H. F. (2005b). Is the early development of girls with Rett disorder really normal? *Pediatric Research, 57*, 696–700.
Einspieler, C., Widder, J., Holzer, A., & Kenner, T. (1988). The predictive value of behavioural risk factors for sudden infant death. *Early Human Development, 18*, 101–109.
Esposito, G., & Venuti, P. (2010). Understanding early communication signals in autism: A study of the perception of infants' cry. *Journal of Intellectual Disability Research, 54*, 216–223.
Fehr, S., Bebbington, A., Nassar, N., Downs, J., Ronen, G. M., De Klerk, N., et al. (2011). Trends in the diagnosis of Rett syndrome in Australia. *Pediatric Research, 70*, 313–319.
Fyfe, S., Downs, J., McIlroy, O., Burford, B., Lister, J., Reilly, S., et al. (2007). Development of a video-based evaluation tool in Rett syndrome. *Journal of Autism and Developmental Disorders, 37*, 1636–1646.
Hagberg, B., Aicardi, J., Dias, K., & Ramos, O. (1983). A progressive syndrome of autism, dementia, and loss of purposeful hand use in girls: Rett's syndrome: Report of 35 cases. *Annals of Neurology, 14*, 471–479.
Kaufmann, W. E., Tierney, E., Rohde, C. A., Suarez-Pedraza, M. C., Clarke, M. A., Salorio, C. F., et al. (2012). Social impairments in Rett syndrome: Characteristics and relationship with clinical severity. *Journal of Intellectual Disability Research, 56*, 233–247.
Keen, D., Woodyatt, G., & Sigafoos, J. (2002). Verifying teacher perceptions of the potential communicative acts of children with autism. *Communication Disorders Quarterly, 23*, 133–142.
Kerr, A. M. (2001). Recent developments in Rett syndrome research. *Current Opinion in Psychiatry, 14*, 437–442.
Kerr, A. M., Archer, H. L., Evans, J. C., & Gibbon, F. (2006). People with mutation positive Rett disorder who converse. *Journal of Intellectual Disability Research, 50*, 386–394.
LaGasse, L. L., Neal, A. R., & Lester, B. M. (2005). Assessment of infant cry: Acoustic cry analysis and parental perception. *Mental Retardation and Developmental Disabilities Research Reviews, 11*, 83–93.
Lavas, J., Slotte, A., Jochym-Nygren, M., Van Doorn, J., & Witt-Engerstrom, I. (2006). Communication and eating proficiency in 125 females with Rett syndrome: The Swedish Rett Center survey. *Disability & Rehabilitation, 28*, 1267–1279.
Luyster, R., Lopez, K., & Lord, C. (2007). Characterizing communicative development in children referred for autism spectrum disorders using the MacArthur–Bates Communicative Development Inventory (CDI). *Journal of Child Language, 34*, 623–654.
Maestro, S., Muratori, F., Barbieri, F., Casella, C., Cattaneo, V., Cavallaro, M. C., et al. (2001). Early behavioral development in autistic children: The first 2 years of life through home movies. *Psychopathology, 34*, 147–152.
Marschik, P. B., & Einspieler, C. (2011). Methodological note: Video analysis of the early development of Rett syndrome – One method for many disciplines. *Developmental Neurorehabilitation, 14*, 355–357.
Marschik, P. B., Einspieler, C., Oberle, A., Laccone, F., & Prechtl, H. F. (2009). Case report: Retracing atypical development: A preserved speech variant of Rett syndrome. *Journal of Autism and Developmental Disorders, 39*, 958–961.
Marschik, P. B., Einspieler, C., Prechtl, H. F., Oberle, A., & Laccone, F. (2010). Relabelling the preserved speech variant of Rett syndrome. *Developmental Medicine and Child Neurology, 52*, 218.
Marschik, P. B., Einspieler, C., & Sigafoos, J. (2012). Contributing to the early detection of Rett syndrome: The potential role of auditory Gestalt perception. *Research in Developmental Disabilities, 33*, 461–466.
Marschik, P. B., Einspieler, C., Garzarolli, B., & Prechtl, H. F. (2007). Events at early development: Are they associated with early word production and neurodevelopmental abilities at the preschool age? *Early Human Development, 83*, 107–114.
Marschik, P. B., Lanator, I., Freilinger, M., Prechtl, H. F., & Einspieler, C. (2011). Early signs and later neurophysiological correlates of Rett syndrome. *Klinische Neurophysiologie, 42*, 22–26.
Marschik, P. B., Pini, G., Bartl-Pokorny, K. D., Duckworth, M., Gugatschka, M., Vollmann, R., et al. (2012). Early speech-language development in females with Rett syndrome: Focusing on the preserved speech variant. *Developmental Medicine and Child Neurology* http://dx.doi.org/10.1111/j. 1469-8749.2012.04123.x.
Matson, J. L., Dempsey, T., & Wilkins, J. (2008). Rett syndrome in adults with severe intellectual disability: Exploration of behavioral characteristics. *European Psychiatry, 23*, 460–465.
Matson, J. L., Fodstad, J. C., & Boisjoli, J. A. (2008). Nosology and diagnosis of Rett syndrome. *Research in Autism Spectrum Disorders, 2*, 601–611.
Mount, R. H., Charman, T., Hastings, R. P., Reilly, S., & Cass, H. (2003). Features of autism in Rett syndrome and severe mental retardation. *Journal of Autism and Developmental Disorders, 33*, 435–442.
Nathani, S., Oller, D. K., & Neal, A. R. (2007). On the robustness of vocal development: An examination of infants with moderate-to-severe hearing loss and additional risk factors. *Journal of Speech, Language and Hearing Research, 50*, 1425–1444.
Neul, J. L., Kaufmann, W. E., Glaze, D. G., Christodolou, J., Clarke, A. J., Bahi-Buisson, N., et al. (2010). Rett syndrome: Revised diagnostic criteria and nomenclature. *Annals of Neurology, 68*, 944–950.
Oller, D. K., Eilers, R. E., Neal, A. R., & Schwartz, H. K. (1999). Precursors to speech in infancy: The prediction of speech and language disorders. *Journal of Communication Disorders, 32*, 223–245.
Ozonoff, S., Iosif, A. M., Young, G. S., Hepburn, S., Thompson, M., Colombi, C., et al. (2011). Onset patterns in autism: Correspondence between home video and parent report. *Journal of American Academy of Child and Adolescent Psychiatry, 50*, 796–806.
Palomo, R., Belinchón, M., & Ozonoff, S. (2006). Autism and family home movies: A comprehensive review. *Developmental and Behavioral Pediatrics, 27*, S59–S68.
Paul, R., Fuerst, Y., Ramsay, G., Chawarska, K., & Klin, A. (2011). Out of the mouths of babes: Vocal production in infant siblings of children with ASD. *Journal of Child Psychology and Psychiatry, 52*, 588–598.
Percy, A. K. (2011). Rett syndrome: Exploring the autism link. *Archives of Neurology, 68*, 985–989.
Percy, A. K., Neul, J. L., Glaze, D. G., Motil, K. J., Skinner, S. A., Khwaja, O., et al. (2010). Rett syndrome diagnostic criteria: Lessons from the Natural History Study. *Annals of Neurology, 68*, 951–955.
Rajaei, S., Erlandson, A., Kyllerman, M., Albage, M., Lundstrom, I., Karrstedt, E. L., et al. (2011). Early infantile onset congenital Rett syndrome variants: Swedish experience through four decades and mutation analysis. *Journal of Child Neurology, 26*, 65–71.
Renieri, A., Mari, F., Mencarelli, M. A., Scala, E., Ariani, F., Longo, I., et al. (2009). Diagnostic criteria for the Zappella variant of Rett syndrome (the preserved speech variant). *Brain and Development, 31*, 208–216.
Robertson, L., Hall, S. E., Jacoby, P., Ellaway, C., de Klerk, N., & Leonard, H. (2006). The association between behavior and genotype in Rett syndrome using the Australian Rett Syndrome Database. *American Journal of Medical Genetics, 141B*, 177–183.
Saint-Georges, C., Cassel, R. S., Cohen, D., Chetouani, M., Laznik, M.-C., Maestro, S., et al. (2010). What studies of family home movies can teach us about autistic infants: A literature review. *Research in Autism Spectrum Disorders, 4*, 355–366.
Siegel-Causey, E., & Guess, D. (1989). *Enhancing nonsymbolic communication interactions among learners with severe disabilities*. Baltimore: Paul H Brookes.
Sigafoos, J., Arthur-Kelly, M., & Butterfield, N. (2006). *Enhancing everyday communication with children with disabilities*. Baltimore: Brookes Publishing Company.
Sigafoos, J., Green, V. A., Schlosser, R., O'Reilly, M. F., Lancioni, G. E., Rispoli, M., et al. (2009). Communication intervention in Rett syndrome: A systematic review. *Research in Autism Spectrum Disorders, 3*, 304–318.
Sigafoos, J., Kagohara, D., van der Meer, L., Green, V. A., O'Reilly, M. F., Lancioni, G. E., et al. (2011). Communication assessment for individuals with Rett syndrome: A systematic review. *Research in Autism Spectrum Disorders, 5*, 692–700.

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

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

Tait, K., Sigafoos, J., Woodyatt, G., O'Reilly, M., & Lancioni, G. (2004). Evaluating parent use of functional communication training to replace and enhance prelinguistic behaviors in six children with developmental and physical disabilities. *Disability & Rehabilitation, 26*, 1241–1254.

Tams-Little, S., & Holdgrafer, G. (1998). Early communication development in children with Rett syndrome. *Brain and Development, 18*, 376–378.

von Tetzchner, S. (1997). Communication skills among females with Rett syndrome. *European Child & Adolescent Psychiatry, 6*, S33–S37.

von Tetzchner, S., Jacobsen, K. H., Smith, L., Skjeldal, O. H., Heiberg, A., & Fagan, J. F. (1996). Vision, cognition, and developmental characteristics of girls and women with Rett syndrome. *Developmental Medicine and Child Neurology, 38*, 212–225.

Wulffaert, J., Van Berckelaer-Onnes, I. A., & Scholte, E. M. (2009). Autistic disorder symptoms in Rett syndrome. *Autism, 13*, 567–581.

Young, D. J., Bebbington, A., Anderson, A., Ravine, D., Ellaway, C., Kulkarni, A., et al. (2008). The diagnosis of autism in a female: Could it be Rett syndrome? *European Journal of Pediatrics, 167*, 661–669.

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

Zappella, M., Meloni, I., Longo, I., Canitano, R., Hayek, G., Rosaia, L., et al. (2003). Study of MECP2 gene in Rettsyndrome variants and autistic girls. *American Journal of Medical Genetics, 119*, 102–107.

Zappella, M., Meloni, I., Longo, I., Hayek, G., & Renieri, A. (2001). Preserved speech variants of the Rett syndrome: Molecular and clinical analysis. *American Journal of Medical Genetics, 104*, 14–22.