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Review article

Regression in Rett syndrome: Developmental pathways to its onset

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ABSTRACT

Rett syndrome (RTT) is an X-linked genetic disorder that occurs predominantly in females. The clinical picture associated with RTT is defined by core and supportive consensus criteria, with a period of behavioural regression being a *conditio sine qua non.* This review sheds light on atypical neurofunctions and potential behavioural biomarkers before the onset of regression. The main focus lies on (a) motor development, especially on purposeful hand movements and the occurrence of stereotypies; and (b) speech-language and socio-communicative development. We outline potentially specific atypical behavioural patterns in these domains (e.g., vocalisations on inspiratory airstream) and different developmental traits of regression: (i) non-achievement of certain milestones: 'regression', here, might point to the fact that the lack of respective behavioural patterns appeared more and more worrisome with increasing age; and (ii) developmental milestones were achieved and functions deteriorate or even get lost during regression. To conclude, we are not quite there yet, but seem to be on the right track towards defining new and reliable neurofunctional markers for early detection of RTT.

1. Introduction

Rett syndrome (RTT; OMIM #312750) is an X-linked genetic disorder that occurs predominantly in females. Its prevalence is estimated at 1:10,000 females, making it one of the most common genetic causes of developmental and intellectual disability (Zoghbi, 2016). RTT is mainly caused by loss-of-function mutations in the gene *MECP2*, which encodes the methyl-CpG-binding protein 2 (MeCP2), a basic nuclear protein highly expressed in the brain (Amir et al., 1999). Mutations in *MECP2* resulting in the loss of MeCP2 entail expression changes in a huge number of genes, dysregulate the neurotransmitter system, and compromise the majority of brain cells and their circuits (Zoghbi, 2016). Armstrong and colleagues found as long ago as 1995 that females with RTT have smaller and more densely packed neurons; their dendritic spines are reduced in length, number, and complexity (Armstrong et al., 1995). We know today that MeCP2 acts as a transcriptional activator and repressor (Chahrour et al., 2008), but also regulates gene expression posttranscriptionally (Cheng et al., 2014) and synaptic activity (Qiu et al., 2012). MeCP2 plays a key role in brain development including prenatal neurogenesis, pre- and postnatal development of synaptic connections and functions, and experience-dependent synaptic maturation and plasticity (Chahrour and Zoghbi, 2007; Kaufmann et al., 2005). MeCP2 is fundamental for the function of various brain circuits by maintaining a critical balance between synaptic excitation and inhibition (Banerjee et al., 2012; Lyst and Bird, 2015; Shepherd and Katz, 2011). Since synaptogenesis and neuronal migration are overlapping processes in human brain development (Tau and Peterson, 2010), MeCP2 may also contribute to cell fate specification and migration (Feldman et al., 2016). Hence, *MECP2* mutations potentially affect prenatal and postnatal brain development as well as adult function (Feldman et al., 2016; Guy et al., 2011). Accordingly, it has been suggested that an earlier onset of symptoms opposes the (apparently) typical early development assumption (e.g., Einspieler et al., 2005a, b; Kerr, 1995; Leonard and Bower, 1998; Marschik et al., 2013b; Naidu et al., 1995; Neul et al., 2010).

The clinical picture associated with RTT is defined by core and supportive consensus criteria (Neul et al., 2010), with a period of behavioural and motor regression being a *conditio sine qua non*. The main features of this period are a partial or complete loss of previously acquired purposeful hand skills and communication skills including spoken language. By that time stereotypic hand movements such as hand wringing and squeezing, clapping, tapping, mouthing and washing and/or rubbing automatism have developed (Hagberg et al., 1985; Neul et al., 2010). Some authors even state that purposeful hand use is "replaced" by stereotypical hand movements (e.g., Katz et al., 2016). During this period, the child's withdrawal from normal social

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exchange accompanied by unmotivated screaming or loud laughter raises parental concern. A definite diagnosis is still missing, leaving the family confused and worried (Lee et al., 2013; Marschik et al., 2012d).

The onset of behavioural regression can be sudden, as a father described: "One day she left hold of her spoon as if it burnt her, then never used her hands again" (Witt-Engerström, 1987; p 483). The most frequently reported pattern of this phenomenon is a gradual process of functional decline over a period of several months or even years which can be difficult to recognize and accompanied by comorbidities (Bisgaard et al., 2015b; Zappella et al., 1998; Zoghbi, 2016).

Studies of medical reports, retrospectively applied checklists, and parental diaries have revealed an onset of regression at the age of 12 to 19 months (Burford et al., 2003; Charman et al., 2002; Fehr et al., 2011; Lee et al., 2013; Witt-Engerström, 1992a), lasting from 6 to 19 months (Witt-Engerström, 1992a). Earlier regression has been reported for females with p.R255X and p.T158 M mutations (Fehr et al., 2011; Lee et al., 2013) and is associated with a more severe phenotype in childand adulthood (Kerr and Prescott, 2005). A late onset of regression, i.e. at the age of 18 months or later, was more often observed in females with p.R133C and p.R294X mutations (Lee et al., 2013; Urbanowicz et al., 2014). The period of regression is generally followed by recovery or stabilisation; the child re-engages with the environment and learning is again possible (Hagberg et al., 1985; Lee et al., 2013).

We are yet to understand the neuropathological mechanism of developmental regression and how the network plasticity deteriorates (Zoghbi, 2016). It can be assumed, however, that regression is not the result of neurodegeneration but arises from altered neuronal function (Pohodich and Zoghbi, 2015). Maternal interviews revealed that sudden strabism, excessive vomiting or inconsolable crying were the first causes for concern. The classical criteria 'loss of hand function' and 'loss of verbal skills' only occurred in a small proportion of children (Lee et al., 2013). By contrast, questionnaires filled in retrospectively by 869 families listed relative frequencies of five functional core features of regression: (a) 87% of the children showed a loss of speech and language function (e.g., loss of babbling, single words, phrases, following commands); (b) the occurrence of stereotypies was 86%; (c) a loss of fine motor skills (e.g., holding a bottle, pincer grasping or finger feeding) was reported for 77% of all individuals; (d) 56% of the patients showed a loss of gross motor behaviours (e.g., pull to sit, crawling, walking); and (e) 20% exhibited a loss of attention (Tarquinio et al., 2015). Similar rates, although in a much smaller sample, had been previously reported by Charman et al. (2002), who were convinced that abnormal signs were already present before regression set in.

Beside classic RTT, a number of variants have been described including the Early Seizure Variant (Hanefeld Variant; mutations in *CDKL5* found in the majority of cases; Bahi-Buisson et al., 2008), the Congenital Variant (Rolando Variant; mutations in *FOXG1* in the majority of cases; Ariani et al., 2008) and the Preserved Speech Variant (PSV-RTT; Zappella Variant, mutations in *MECP2* found in the majority of cases; Neul et al., 2010), the latter of which is probably the most common. Some form of regression is also required for a PSV-RTT diagnosis (Neul et al., 2010), which has a better overall pathogenesis, including better manual and speech-language abilities than in classic RTT (Marschik et al., 2009b; Renieri et al., 2009; Zappella, 1992).

1.1. Is it fair to describe the development before the regression period as normal?

The Austrian paediatrician Andreas Rett was convinced that his patients had achieved early developmental milestones, some of them even precociously (Rett, 1966, 2016). He described all 22 children in his first report on RTT as healthy until at least 9 months, although nine of them had considerable feeding difficulties during early infancy. In view of the gravity of later signs and symptoms, Hagberg et al. (1985) listed an 'early normal development' as one of the diagnostic core criteria. Based on parental interviews and inspection of medical histories, several clinicians raised their doubts and suspected that early development might already be compromised (Kerr and Stephenson, 1986; Kerr et al., 1987; Nomura and Segawa, 1990; Nomura et al., 1984, 1985; Opitz and Lewin, 1987). The Swedish paediatrician Ingegerd Witt-Engerström (1987) described her motivation to explore the early history of children later diagnosed with RTT as based on the frustration of parents who had tried to describe behavioural changes in their children to health care professionals but had usually been told that everything was fine. Indeed, medical reports revealed first neurological dysfunctions at 8–10 months, when upright equilibrium reactions were vague or deficient. By 15 months, development had stagnated in eight of ten children, and circulating hand-mouth movements had co-occurred with a diminished social interest (Witt-Engerström, 1987). Alison Kerr became more and more convinced that children with RTT hit their developmental ceiling around 9–12 months (Kerr, 1995; Kerr et al., 1987). Retrospective parental inquiries revealed that approximately half of the parents had already suspected their child's development to be unusual during the first 6 months of life. The most common comments were that the infant was remarkably placid, slept too well, had to be woken for feeds, or had an empty gaze. Some parents also reported feeding problems; others were concerned about abnormal crying and a delay in reaching developmental milestones (Charman et al., 2002; Kerr et al., 1987, 2001; Leonard and Bower, 1998; Naidu, 1997; Naidu et al., 1995; Nomura and Segawa, 1990; Nomura et al., 1984, 1985; Witt-Engerström, 1987, 1992a, 1992b). These observations finally led to a consensus meeting in 2001 at the European Paediatric Society conference in Baden Baden, Germany, where the diagnostic clinical criteria were revised. Part of the consensus was that early normality would no longer be regarded as mandatory for a classic RTT diagnosis (Hagberg et al., 2002). In the consensus paper of 2010, Neul and colleagues stated that "some alterations in initial development can be present" but "typically the family and the primary clinician is not concerned about development until after 6 months o fife." (Neul et al., 2010, p. 947).

Early parental concerns that "something was wrong" long before regression occurred were confirmed by more recent studies (Bisgaard et al., 2015a; Fehr et al., 2011). Although concerns were partly related to medical issues like sudden squinting or severe reflux, observations of excessive quietness especially during the first 6 months of life were worrisome for a considerable number of parents (Bisgaard et al., 2015a; Fehr et al., 2011). But to what extent are such subtle developmental deviations specific to RTT? Similar observations have been made by parents whose infant died suddenly and unexpectedly (Einspieler et al., 1988). How much weight can be given to retrospective diagnoses of past events if we take into consideration an exaggerated recollection of distant problems?

In the mid 1990s, the analysis of family films recorded at a time when parents or caregivers had not been aware of their child's disorder became increasingly popular representing a methodological advancement and valuable source of information. Alison Kerr's initial assessments of family footage in 1995 left her convinced that young infants later diagnosed with RTT might have exhibited some sort of incompetence rather than simply failing to fulfil particular tasks. Approximately eight years later she asked Heinz Prechtl and the first author of the present article (C.E.) to analyse 17 video clips (eight of females with RTT and nine of typically developing children) taken by parents during their daughters' first 6 months of life. Blinded to the developmental outcome, we were able to distinguish all infants with subsequent RTT diagnoses from typically developing infants (Einspieler et al., 2005b). This encouraging result was the starting point for numerous meticulous observations and analyses of early motor and sociocommunicative behaviours (see Tables 1–3 for all related references) and would ultimately also include automatic analyses of aberrant early neurofunctions based on signal-analytical and machine-learning approaches (Pokorny et al., 2016, 2018; Marschik et al., 2017).

As one striking example of the insight to be gained into the

Table 1
Emergence of hand stereotypies during the pre-regression period in infants and toddlers later diagnosed with RTT or its PSV and method applied.

(Case) Mutation	Age of onset	Age of regression	Description of hand stereotypies	Method	
(1) p.T158M	2 months	around 24 months	uni- or bilateral repetitive pronation of the hand with simultaneous dorsiflexion of the wrist; uni- or bilateral excessive repetitive opening and closing of both hands, sometimes with synchronised plantar flexion of the toes; repeated bringing of the palmar sides of both hands together, raising both hands, and separating them again.	RVA, 94% agreement	Einspieler et al., 2005a
(2) p.Q244X	2 months	around 24 months			
(3) p.R168X	4 months	around 24 months			
(4) *MECP2* pos.	4 months	around 24 months			
(5) *MECP2* neg.*	4 months	around 24 months			
(6) not tested	4 months	around 24 months			
(7) not tested	4 months	around 24 months			
(8) not tested	4 months	around 24 months			
PSV-RTT,	6.5 months	24 months	Repetitive uni- or bilateral hand pronation with simultaneous wrist dorsiflexion and finger spreading.	RVA, Kappa = 0.91	Marschik et al., 2009a
(9) c.378-43_964delinsGA	16 months		Wiping hand movements		
(10) c.378-?*del	7 months	10 months	Abnormal hand movements	Medical history / parental report	Bisgaard et al., 2015a
(11) p.R168X	12 months	20 months			
(12) p.T158M	14 months	15 months			
(13) c.806delG	18 months	20 months			
PSV-RTT			Repetitive uni- or bilateral hand pronation with simultaneous wrist dorsiflexion	RVA, Kappa = 0.92	Marschik et al., 2012c
(14) p.R133C	7 to 18 months	> 24 months			
(15) p.R133C	7 to 18 months	> 24 months			
(16) p.R133C	7 to 18 months	> 24 months			
(17) p.C468G	7 to 18 months	> 24 months			
(9) c.378-43_964delinsGA, (18) c.1163del44	7 to 18 months	> 24 months			
(19) p.R133C	9 months	18 months	Hand flapping	Maternal report (interview)	Lee et al., 2013
(20) p.T158M	12 months	14 months	n.a.		
(21) p.R133C	15 months	34 months	Repetitive hair pulling		
(22) p.R294X	18 months	36 months	n.a.		
(23) not tested	13 months	not given	Repetitive patting with the dorsum of the hand to the mouth; repetitive opening and closing of the right hand with pronation and dorsiflexion of the wrist	RVA, Kappa = 0.94	Einspieler et al., 2014a
(24) p.R270X	19 months	22 months	Repetitive dystonic movements with her right limbs; finger twisting; washing-like movements; clapping; twirling; hand to mouth movements	concurrent video observation	Temudo et al., 2007a

Key: n.a. = not available, RVA = retrospective video analysis; *Females clinically diagnosed as RTT but labelled as *MECP2* negative until 2005. Possibly sequencing at that time had been focussed on the coding region, while in fact there may have been mutations in the regulatory control regions (Zoghbi, 2016). It is possible, therefore, that some of them had a *MECP2* mutation which was not identified at the time.

Table 2
Typical and atypical socio-communicative and (pre)linguistic behaviours in females with classic RTT before regression and method applied.

Observed/Reported behaviour	Typical/Age band	Atypical/Age band	Method Total N, *MECP2* mutation in individuals with reported behaviour, analysis, reliability	
SOCIO-COMMUNICATIVE MILESTONES				
Eye contact	present 1 to 6 months n = 22/22	asymmetrical eye opening; 1 to 6 months n = 10/22	N = 22, p.T158 M, p.Q244X, p.168X, R168X, n.a. (n = 4), RVA, 93% agreement	Einspieler et al., 2005a
	present 9 to 12 months n = 6/6		N = 6, *MECP2* positive, RSV, 87% agreement	Bartl-Pokorny et al., 2013
	present 9 to 24 months n = 1/1		N = 1, p.R168X, RVA, 93% agreement	Marschik et al., 2013a
Responsive smile	not given	frozen, bizarre, inadequate 2 to 6 months n = 6/22	N = 22, p.Q244X (two), p.T158 M, p.R168X, not tested, negative* (n = 2), RVA, 94% agreement	Einspieler et al., 2005a
	present 8 to 24 months n = 2/2	interspersed with frozen smiling movements n = 2/2	N = 2 (monozygotic twins), not tested, RVA, Kappa = 94	Einspieler et al., 2014a
	present 9 to 12 months n = 5/6	absent 9 to 12 months n = 1/6	N = 6, *MECP2* positive, RSV, 87% agreement	Bartl-Pokorny et al., 2013
	present 9 to 24 months n = 1/1		N = 1, p.R168X, RVA, 93% agreement	Marschik et al., 2013a
	present first year n = 8/16	absent first year n = 8/16	N = 16, n.a., maternal questionnaire	Nomura and Segawa, 1990
Reaction to being called by name	present 5 to 24 months n = 10/10	continuously declining with age	N = 10, *MECP2* positive, RSV, 93% agreement	Townend et al., 2015; Zhang et al., 2018a, 2018b
	present first year n = 5/16	absent first year n = 9/16	N = 16, n.a., maternal questionnaire	Nomura and Segawa, 1990
	present 12 months n = 1/2	absent 21 months n = 1/2	N = 2 (monozygotic twins), not tested, RVA, Kappa = 94	Einspieler et al., 2014a
PRE-LINGUISTIC VOCALISATIONS				
Cooing	age-adequate n = 7/10	never observed, n = 3/10	N = 10, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b
		never observed 1 to 24 months n = 2/2	N = 2 (monozygotic twins), not tested, RVA, Kappa = 0.94	Einspieler et al., 2014a
(Modulated) vocalisations on inspiratory airstream		3 to 12 months n = 7/10	N = 10, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b
Pressed vocalisations with strained voice quality		9 months n = 1/2	N = 2, not tested, RVA, Kappa = 0.94	Einspieler et al., 2014a
Pleasure vocalisations	present 9 to 12 months n = 2/6	never observed 9 to 12 months n = 4/6	N = 6, *MECP2* positive, RSV, 87% agreement	Bartl-Pokorny et al., 2013
	present 9 to 24 months n = 1/1		N = 1, p.R168X, RVA, 93% agreement	Marschik et al., 2013a
Babbling (canonical and variegated)		never observed 9 to 24 months n = 1/1	N = 1, p.R168X, RVA, 93% agreement	Marschik et al., 2013a
		never observed 9 to 12 months n = 6/6	N = 6, *MECP2* positive, RSV, 87% agreement	Bartl-Pokorny et al., 2013
		never observed 1 to 24 months n = 2/2	N = 2 (monozygotic twins), not tested, RVA, Kappa = 0.94	Einspieler et al., 2014a
	age-adequate n = 5/10	never observed n = 5/10	N = 10, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b
	present first year n = 7/16	absent first year n = 9/16	N = 16, n.a., maternal questionnaire	Nomura and Segawa, 1990
		never observed first 2 years n = 2/2	N = 2 (monozygotic twins), not tested, RVA, Kappa = 94	Einspieler et al., 2014a
GESTURES				
Index finger pointing		never observed 9 to 24 months n = 1/1	N = 1, p.R168X, RVA, 93% agreement	Marschik et al., 2013a

(*continued on next page*)

Table 2 (*continued*)

Observed/Reported behaviour	Typical/Age band	Atypical/Age band	Method Total N, *MECP2* mutation in individuals with reported behaviour, analysis, reliability	
	9 to 18 months n = 2/7	never observed n = 5/7	N = 7, *MECP2* mutation pos., RVA, n.a.	Marschik et al., 2012d
	present first year n = 2/16	absent first year n = 14/16	N = 16, n.a., maternal questionnaire	Nomura and Segawa, 1990
Waving bye bye	present 9 to 18 months n = 1/1		N = 1, p.R168X, RVA, 93% agreement	Marschik et al., 2013a
	present 9 to 18 months n = 1/7	absent 9 to 18 months n = 6/7	N = 7, *MECP2* mutation pos., RVA, n.a.	Marschik et al., 2012d
Extending arms seeking comfort	present 9 to 18 months n = 7/7		N = 7, *MECP2* mutation pos., RVA, n.a.	Marschik et al., 2012d
	present 13 to 18 months n = 1/1		N = 1, p.R168X, RVA, 93% agreement	Marschik et al., 2013a
Demonstrating an object	present 9 to 18 months n = 5/7	absent 9 to 18 months n = 2/7	N = 7, *MECP2* mutation pos., RVA, n.a.	Marschik et al., 2012d
Shaking the head indicating “no”	present 9 to 18 months n = 4/7	absent 9 to 18 months n = 3/7	N = 7, *MECP2* mutation pos., RVA, n.a.	Marschik et al., 2012d
Passing an object	present 9 to 18 months n = 2/7	absent 9 to 18 months n = 5/7	N = 7, *MECP2* mutation pos., RVA, n.a.	Marschik et al., 2012d
	present 13 to 18 months n = 1/1		N = 1, p.R168X, RVA, 93% agreement	Marschik et al., 2013a
LINGUISTIC VOCALISATIONS				
Proto-words and words		never observed 9 to 24 months n = 1/1	N = 1, p.R168X, RVA, 93% agreement	Marschik et al., 2013a
		never observed 9 to 12 months n = 6/6	N = 6, *MECP2* positive, RVA, 87% agreement	Bartl-Pokorny et al., 2013
	age-adequate n = 3/10	never observed n = 7/10	N = 10, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b
	age-adequate n = 16/20	not acquired n = 4/20	N = 20, n.a., personal examination, interviews with parents and medical staff	Witt-Engerström, 1992a
Two-word combinations		never observed n = 10/10	N = 10, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b
	age-adequate n = 1/20	not acquired n = 19/20	N = 20, n.a., personal examination, interviews with parents and medical staff	Witt-Engerström, 1992a

Key: n.a. = not available (in some cases the publication preceded the description of the responsible gene); RVA = retrospective video analysis.

* Females clinically diagnosed as RTT but labelled as *MECP2* negative until 2005. For comment, see legend to Table 1.

complexity of potential deviations we would like to point out the trajectory of a child diagnosed with PSV-RTT at 3 years of age, where we found that perfectly normal babbling was interspersed with abnormal vocalisations (Marschik et al., 2009a, 2009b; Pokorny et al., 2016, 2018). In addition, video recordings taken between 9 and 12 months showed very skilful pincer grasping suddenly interrupted by hand stereotypies (Marschik et al., 2009a), which became more and more obvious when the child approached the period of regression at 2 years of age (Marschik et al., 2014).

Detailed documentation of early dysfunctions in children with RTT is largely still based on single cases or small samples. Unlike detailed analyses of existing footage (audio-video recordings, mostly), the so far largest natural history study based on parental interviews revealed that 99% (645/653) of females with classic RTT had developed normally in early infancy. All of them had acquired fine motor and communication skills, which they lost during the period of regression, and all of them developed hand stereotypies (Percy et al., 2010). Only a small group (8/653; 1%) had shown minor prenatal, perinatal or early developmental deviations, but no significant problems that might have indicated neurological dysfunction.

1.2. How to shed light on the development before the onset of regression

The diagnosis of classic RTT is still tentative until a median age of 3 years, with an interquartile range of 2–4 years, and is vague until a little more than a year later in case of PSV-RTT (Bisgaard et al., 2015a; Cianfaglione et al., 2015; Tarquinio et al., 2015). Therefore, and because this is a rare disease, our possibilities to track down pre-diagnostic development, to say nothing of neurofunctions before regression, are limited. Hence, retrospective studies based on parental reports (interviews, questionnaires, but also parental diaries and medical histories) and/or analyses of family videos are currently the method of choice, albeit a limited one.

The results of retrospective parental questionnaires and/or interviews may be tinted by a (significant) time lag between the interview and the actual period of interest, by memory bias of parents (who are aware of the diagnosis by the time they are interviewed), by telescoping or similar effects observed in post-hoc reporting. We also need to consider the lack of parental training in observing and reporting particular developmental features, especially with regard to the quality of performance (Marschik and Einspieler, 2011; Einspieler et al., 2016; Zhang et al., 2018a). Parents may be able to memorise reliably *whether*

Table 3
Typical and atypical socio-communicative and (pre)linguistic behaviours in females with PSV-RTT before regression and method applied.

Observed/Reported behaviour	Typical/Age band	Atypical/Age band	Method Total N, *MECP2* mutation in individuals with reported behaviour, analysis, reliability	
SOCIO-COMMUNICATIVE MILESTONES				
Eye contact	present 9 to 24 months n = 1/1		N = 1, c.378-43_964delinsGA, RVA, 93% agreement	Marschik et al., 2013a
Responsive smile	present 13 to 24 months n = 1/1		N = 1, c.378-43_964delinsGA, RVA, 93% agreement	Marschik et al., 2013a
PRE-LINGUISTIC VOCALISATIONS				
Cooing	age-adequate n = 5/5		N = 5, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b
(Modulated) vocalisations on inspiratory airstream		3 to 12 months n = 2/5	N = 5, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b
Communicative dysfunction not further specified		from 6 months onwards n = 1/1	N = 1, n.a. parental report and medical history	Zappella, 1994
		6 months n = 1/1	N = 1, c.378-43_964delinsGA, RVA, 93% agreement	Marschik et al., 2013c
		7 to 12 months n = 3/6	N = 6, n.a., RVA, Kappa = 0.92	Marschik et al., 2012c
Babbling (canonical and variegated)	present 7 to 12 months n = 4/6	absent 7 to 12 n = 2/6	N = 6, p.R133C (n = 3), C468 G, c.378-43_964delinsGA, c.1163del44, RVA, Kappa = 0.92	Marschik et al., 2012c, 2013c
	age-adequate n = 4/5	never observed n = 1/5	N = 5, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b
Pressed vocalisations		7 to 24 months n = 6/6	N = 6, p.R133C (n = 3), C468 G, c.378-43_964delinsGA, c.1163del44, RVA, Kappa = 0.92	Marschik et al., 2012c
High-pitched crying-like vocalisations		7 to 24 months n = 6/6	N = 6, p.R133C (n = 3), C468 G, c.378-43_964delinsGA, c.1163del44, RVA, Kappa = 0.92	Marschik et al., 2012c
GESTURES				
Index finger pointing	present 10 to 24 months n = 1/1		N = 1, c.378-43_964delinsGA, RVA, 93% agreement	Marschik et al., 2009a; 2013a
	present 12 to 24 months n = 2/5	never observed 12 to 24 months n = 3/5	N = 5, c.1163del44, c.378-43_96delinsGA, RVA, Kappa = 0.86	Marschik et al., 2012b
Waving bye bye	present 12 to 24 months n = 3/5	never observed 12 to 24 months n = 2/5	N = 5, p.R133C, p.R133C, c.378-43_96delinsGA, RVA, Kappa = 0.86	Marschik et al., 2012b
	present 13 to 18 months n = 1/1		N = 1, c.378-43_964delinsGA, RVA, 93% agreement	Marschik et al., 2013a
Extending arms seeking comfort	present 12 to 24 months n = 5/5		N = 5, p.R133C, C468 G, p.R133C, c.1163del44, c.378-43_96delinsGA, RVA, Kappa = 0.86	Marschik et al., 2012b, 2013a
Demonstrating an object	present 9 to 18 months n = 1/1		N = 1, c.378-43_964delinsGA, RVA, 93% agreement	Marschik et al., 2013a
Shaking the head indicating “no”	present 12 to 24 months n = 2/5	never observed 12 to 24 months n = 3/5	N = 5, c.1163del44, c.378-43_96delinsGA, RVA, Kappa = 0.86	Marschik et al., 2012b, 2013a
Head nodding indicating “yes”	present 12 to 24 months n = 1/5	never observed 12 to 24 months n = 4/5	N = 5, c.1163del44, RVA, Kappa = 0.86	Marschik et al., 2012b
Passing an object	present 12 to 24 months n = 1/1		N = 1, c.378-43_964delinsGA, RVA, 93% agreement	Marschik et al., 2013a
Sending kisses	present 19 to 24 months n = 1/1		N = 1, c.378-43_964delinsGA, RVA, 93% agreement	Marschik et al., 2012b, 2013a
LINGUISTIC VOCALISATIONS				
Proto-words and words	present 9 to 24 months n = 1/1		N = 1, c.378-43_964delinsGA; RVA, 93% agreement	Marschik et al., 2009a, 2013a
	present until 18 months n = 4/6	absent 12 to 18 months n = 2/6	N = 6, p.R133C (n = 3), C468 G, c.378-43_964delinsGA, c.1163del44, RVA, Kappa = 0.92	Marschik et al., 2012c
	present < 12 months n = 1/1		N = 1, n.a., parental report and medical history	Zappella et al., 1998
	present during 12th month n = 1/1		N = 1, n.a., parental report and medical history	Zappella, 1994

(*continued on next page*)

Table 3 (*continued*)

Observed/Reported behaviour	Typical/Age band	Atypical/Age band	Method Total N, *MECP2* mutation in individuals with reported behaviour, analysis, reliability	
	age-adequate n = 3/5	never observed n = 2/5	N = 5, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b
Perseveration of more than 20 consecutive unconventional vocalisations		12 to 24 months n = 1/1	n = 1, c.378-43_964delinsGA, RVA, 93% agreement	Marschik et al., 2013c
Two-word combinations	age-adequate n = 1/5	never observed n = 4/5	N = 5, *MECP2* positive, RVA, 97% agreement	Marschik et al., 2013b

Key: n.a. = not available (in some cases the publication preceded the description of the responsible gene); RVA = retrospective video analysis.

their child acquired a certain behaviour, but are mostly unable to recall, let alone describe, *how* and *when* this behaviour manifested itself.

This makes the analysis of family videos recorded at a time when the parents or caregivers were not yet aware of their child's disorder a more reliable option to focus on early behaviours. One of its strengths lies in the possibility of meticulously describing observable phenomena and behavioural peculiarities. Drawbacks of the method include the fact that particular behaviours might not be observable in the available dataset, although they might have been present in real life (Marschik and Einspieler, 2011). Home videos are not usually recorded for the purpose of later scientific analysis; settings are not standardised, since parents are keen to videotape events for (pleasant) memory. The quality of recordings, the amount of material, and sometimes even the ability to determine the precise age can vary considerably. And yet, while some peculiar behaviours or abnormalities go unnoticed by parents, they do not escape the eye of the camera (Marschik and Einspieler, 2011). Video analyses allow us to focus on the emergence and quality of certain behaviours (though the exact age often remains uncertain).

One shortcoming of both methodological approaches – retrospective parental reports and video footage – is the lack of comparative data. As home videos are not set in standardised situations, it remains difficult to compare the results of observation and assessment between different contrast groups, even if they are present in a particular data set (Marschik et al., 2013a; Roche et al., 2018; Zhang et al., 2018b). Though this would have been easily feasible, most studies based on parental questionnaires (e.g. Fehr et al., 2010, 2011; Leonard et al., 2005; Neul et al., 2014) have failed to include a control group. Just think of how many happy and unsuspecting parents of (supposedly) typically developing infants find their child to be a "very placid and easily satisfied infant" (Leonard et al., 2005, p. 63) during the first half year of life, or might, conversely, observe stereotypical movements that are actually typical of a certain age and represent a normal development (Thelen, 1979, 1981)!

Prospectively collected data have no doubt certain advantages over retrospective designs. In rare developmental disorders, prospective data collection is mainly feasible in cohort studies. For example, a nationwide Danish birth cohort study revealed that none of the six females diagnosed with RTT had achieved a productive vocabulary of more than 10 words by the age of 18 months. Note that the parents reported the same of the majority of toddlers (58%; n = 36.292) in the cohort (Marschik et al., 2018). This is an interesting finding, because the birth cohort approach is not principally designed for detecting early markers of developmental disorders: it does not allow for detailed analyses of developmental domains or individual assignment of data and doesn't cover many fields of interest.

In a word: while *the* ideal method for studying early pre-diagnostic development in RTT is yet to be found, video recordings at least allow us to observe typicalities and neurofunctional peculiarities with some accuracy and attention to detail. Retrospective video analysis has also changed over time, abandoning the purely descriptive pathway in favour of experimental designs including expert or caregiver ratings and signal analytical approaches (e.g., Burford et al., 2003; Marschik et al., 2012a, 2017; Pokorny et al., 2018).

1.3. The aim of this review

The aim of this review is to shed light on the development of females with RTT before the onset of regression by focussing on neurofunctions whose loss is a prerequisite for a RTT diagnosis: (a) purposeful hand movements, and (b) acquired speech-language and socio-communicative abilities. A biological definition of regression in terms of a return to a previous, less advanced state, condition or behaviour implies that a function can only be *lost* if it was acquired before. Furthermore, a better understanding of very early behavioural deviations might help us to unravel the significance of *MECP2* and its mutations for the developing organism.

2. Search strategy

A systematic search (September 30, 2018) was conducted in the following electronic data bases: PubMed, Medline, Web of Science, PsycINFO, Google Scholar, and Scopus. Search terms were briefed to target studies on RTT with a focus on early development, pre-diagnostic development, and regression. The search was restricted to peer-reviewed articles published in English. Ancestry searches of included articles and systematic reviews were subsequently conducted. Our review focusses on detailed descriptions of relevant neurofunctions including fine motor skills and (hand)stereotypies as well as speech-language and socio-communication in females with classic RTT and PSV-RTT before the onset of regression. Other variants of RTT (congenital and early seizure) are characterised by abnormal features during the first months of life (Huppke et al., 2003) and are therefore not included in this review. We also excluded reports on males with RTT, as the majority of published cases are more severely affected, usually resulting in severe neonatal encephalopathy and frequent lethality during infancy (Chahrour and Zoghbi, 2007).

3. Development and regression in different behavioural domains

3.1. Motor development with a focus on fine motor functions

According to family questionnaires, 80–90% of infants later diagnosed with RTT were able to sit without support (Fehr et al., 2011; Huppke et al., 2003; Neul et al., 2014), although some did not achieve this milestone before the age of 30 months (Fehr et al., 2011). Independent walking was achieved by 46% (Fehr et al., 2011) to 53% (Neul et al., 2014) of infants, though also with a delay in half of the patients (Fehr et al., 2011). It remains a remarkable finding that none of the 25 infants (later diagnosed with RTT or PSV-RTT) who were assessed for endogenously generated general movements during the first 4 months of life (General Movement Assessment, GMA; Einspieler and Prechtl, 2005; Prechtl et al., 1997) achieved a normal score (Einspieler et al., 2005a, 2005b, 2014a, 2014b; Marschik et al., 2009a), which is an integrity marker of the developing nervous system. However, no specific abnormal general movement pattern for RTT could be identified (Einspieler et al., 2014b).

Here, we focus on the fine motor development of infants later

diagnosed with RTT or PSV-RTT. Analysing videos of 22 infants recorded during the first 6 months of life, Einspieler et al. (2005a) observed abnormal finger movements in half of the cases assessed. Some infants showed continuous fisting until 4 months, others excessive finger spreading or abnormal bilateral, synchronised opening and closing of all fingers. By the age of 5 or 6 months, a third of the infants touched toys with extended fingers without manipulating them (Einspieler et al., 2005a). One girl with a later diagnosis of PSV-RTT touched objects with her fingers mainly extended, performing undifferentiated movements (Marschik et al., 2009a). Monozygotic twins with RTT even fisted until 10 months or longer; finger movements were sporadical and with limited variability (Einspieler et al., 2014a). Health visitors and midwifes who watched family videos taken during the infants' first 12 months of life commented extensively on clenched, crossed, or spread fingers (Burford et al., 2003).

More than 30 years ago, Witt-Engerström (1987) found RTT to be affecting arm and hand movements before certain hand skills were lost. She documented that only 11/20 infants had acquired to pincer grasp, and only 7/20 had displayed finger feeding (Witt-Engerstöm, 1992a,b). The British Isles Survey for Rett Syndrome also documented the absence of hand use such as finger feeding or drinking from a mug before the period of regression (Kerr and Prescott, 2005). And a natural history study (Neul et al., 2014) revealed that 9 to 26% of 542 children were never able to transfer objects, hold a bottle, pincer grasp or finger feed. It is important to note that the majority of children who acquired these milestones did so with a delay.

In a prospective cohort study including 62,624 toddlers a checklist assessment at the age of 18 months revealed that none of the six females later diagnosed with RTT were able by that age to fetch objects and take them to others. This fine motor behaviour was observed in 97% of the total cohort (Marschik et al., 2018).

3.2. First occurrence of (hand) stereotypies

In the very issue of the Brain Development journal in which Witt-Engerström declared her suspicion of peculiar arm and hand movements in the pre-regression period, Kerr et al. (1987) discussed the possibility of pre-regression stereotypies, as they had observed repetitive limb and trunk movements in family videos. A year earlier, Kerr and Stephenson (1986) had already described early repetitive opening of the hand as though the infant had sought to grasp. Likewise, Nomura and Segawa (1990) reported autostimulation behaviour in 11/14 infants during the first year. Einspieler et al. (2005a) observed the earliest body stereotypies, namely side-to-side body rocking while simultaneously shaking or nodding the head at 5 months (one infant with p.R168X mutation; one infant was only clinically diagnosed).

Hand stereotypies are considered to be markers of the period of regression, co-occurring with a deterioration of manipulative skills. Typical hand stereotypies in patients with RTT were first described as hand washing, pressing the hands together in front of the chest or chin, and mouthing the hand (Olsson and Rett, 1987; Rett, 1966, 2016). Furthermore, wringing, squeezing, mouthing, rubbing, scratching, wriggling, twirling, twiddling, knitting, stroking, kneading, clapping or flapping along the midline added to the picture of hand stereotypies (e.g., Elian and Rudolf, 1996; Hagberg et al., 1983; Temudo et al., 2007a, 2007b). Elian and Rudolf (1996) observed that 11/25 (44%) individuals displayed a different pattern in each hand. For example, the left hand twiddled with clothes while the right hand tapped on the forehead. Stereotypies in atypical RTT seemed to vary even more (Wong et al., 2017).

But when do hand stereotypies start to appear? About half of 580 families (Australian Rett Syndrome and InterRett Databases) stated that hand stereotypies had emerged at around 27 months (mean age). Furthermore, they reported that their daughters had developed hand stereotypies prior to the loss of hand function (Fehr et al., 2011). One third of the children had reportedly shown hand stereotypies before the age of 18 months. With increasing age, some stereotypies like clapping or mouthing became less prevalent, while hand wringing was unrelated to age (Carter et al., 2010). According to Lee et al. (2013), hand stereotypies were already frequent and intense by the age of 15 months and had developed prior to a loss of hand functions in 8/14 females. Video analyses also revealed that the onset of stereotypies can precede the loss of purposeful hand movements (Temudo et al., 2007a, 2007b). Bear in mind that Witt-Engerström (1987, p. 483) had described a toddler whose "simple hand use alternated with repetitive hand-mouth circling" for several months before hand use ceased.

Consequently, the questions arise whether hand stereotypies can already occur during the first year of life, and in what form. In 1987, Opitz and Lewin stated that "Hanefeld also expresses his view that Rett syndrome girls probably are not normal at birth and may then already have a 'dyskinetic' disturbance of hand movements" (Opitz and Lewin, 1987, p. 448). And sure enough, 18 years later 5 out of 320 families taking part in a parental questionnaire study explicitly mentioned that their daughter had already shown a strange hand behaviour during the first 6 months of life (Leonard et al., 2005). At the same time an analysis of 22 infants videotaped during the first 6 months of life came to the surprising result that hand stereotypies were clearly recognizable in eight infants (36%). Two of them had even shown stereotypical hand movements during the first 2 months. The hand stereotypies mostly consisted of repetitive opening and closing of the hand, repetitive twisting movements of the wrists and arms, and uni- or bilateral repetitive supination/pronation of the hand(s) with simultaneous dorsiflexion of the wrist(s). One child repeatedly put together her hands, raised them in a kind of praying position, and separated them again (Table 1; Einspieler et al., 2005a; Marschik et al., 2012c). It must be noticed, however, that these stereotypies were interspersed with a variety of normal and purposeful hand movements and postures (Einspieler et al., 2005a, 2016; Marschik et al., 2009a).

In all seven studies taken together, hand stereotypies before the onset of regression were identified in a total of 24 children (Table 1). The hand stereotypies were observed at a median age of 7 months, i.e. 17 months (median) before the period of regression set in. The earliest onset of hand stereotypies was videotaped at 2 months (Cases 1 and 2), i.e. no less than 22 months before the first signs of regression appeared. The shortest time lag between the emergence of hand stereotypies and the onset of regression was 1 month (Case 12). The latest occurrence of hand stereotypies before regression was at 19 months (Case 24). By the time of publication, four females (Cases 6, 7, 8 and 23) were not yet tested for mutation, and one was documented as *MECP2* negative. Surprisingly, five females with hand stereotypies emerging at 7, 9 or 15 months had a p.R133C mutation, contrary to literature reports about a late onset of hand stereotypies in females with this mutation (Fehr et al., 2011). Case 22, who had a p.R294X mutation, showed stereotypies starting at 18 months; her late onset of regression at 36 months is in line with literature (Fehr et al., 2011). Recently, Wong et al. (2017) reported that females with p.T158 M, p.R168X, p.R270X, p.R106 W, or pR294X had a larger variety of hand stereotypies. The careful documentation of 24 children in Table 1 does not include a genotype-phenotype comparison, but the description of stereotypies shows that almost every infant exhibited different patterns of stereotypy. Apparently such inter- and intra-individual variations add to the difficulty of an operational definition of hand stereotypies (Dy et al., 2017).

Finally, we would like to emphasise that typically developing infants might also show a variety of rhythmical or even stereotyped behaviours involving the hand and fingers, as well as the legs, head and trunk in various postures. Esther Thelen (1979, 1981) proposed that these phylogenetically old movements are manifestations of incomplete cortical control of endogenously generated patterns and may even be necessary for the maturation of neuromuscular pathways. Abnormal hand stereotypies, however, might be the result of altered activities in the cortico-striato-thalamo-cortical loop (Gao and Singer, 2013; Kates et al., 2005).

3.3. Early socio-communicative development

Early behaviours related to socio-communicative development comprise eye-contact, responsive smiling, pre-linguistic vocalisations (cooing, babbling), and gestures to express wants and needs. By the end of the first year of life or the beginning of the second, first (proto)words are produced. Thirty carefully documented individual trajectories (five studies) revealed that all infants later diagnosed with RTT or PSV-RTT had eye contact before regression (Tables 2 and 3). Although the related natural history study documented responsive smiling in almost all infants (Neul et al., 2014), one of the earliest studies on early behavioural signs showed that responsive smiling was absent in 8/16 infants (Nomura and Segawa, 1990). Video analysis of 22 infants recorded during their first 6 months of life highlighted another interesting aspect: frozen, bizarre and inadequate smiling occurred in six infants at 2.5 and 6 months (Einspieler et al., 2005a). Furthermore, a pair of monozygotic twins with RTT showed normal social smiling interspersed with smiling movements during the age band of 8–24 months (Einspieler et al., 2014a).

A reduced interest in objects and social contacts may occur during the period of regression even if eye contact is maintained. However, some parents have reported pre-regression social peculiarities such as not recognizing familiar adults (Charman et al., 2002). Social reciprocity can be reliably studied from family videos by assessing a child's response to being called by name. Twenty-six documented cases were available (Table 2): while ten (38%) children did not respond to their name being called (Einspieler et al., 2014a; Nomura and Segawa, 1990), the responsiveness of the remaining 16 children declined with increasing age (Townend et al., 2015; Zhang et al., 2018b).

3.4. Atypicalities in cooing and babbling are indicators of an altered development

Pre-linguistic vocalisations emerge during the first months of life and progress and change continually in appearance, frequency and variability (Karmiloff and Karmiloff-Smith, 2009). More precisely, between approximately 6 and 10 months of age, cooing gradually disappears and early marginal babbling sets in, followed by more complex canonical syllable and babbling sounds or even variegated babbling (e.g. Nathani et al., 2006; Oller et al., 1999). A study on a smaller sample (Tams-Little and Holdgrafer, 1996), as well as some large-scale natural history and data- base studies on RTT concluded that almost all children had acquired cooing and babbling (Neul et al., 2014; Urbanowicz et al., 2014). However, we need to consider that these studies were based on parental interviews given a considerable number of years after the period of interest, and that it might be difficult for parents to remember accurately or indeed identify pre-linguistic cooing or babbling vocalisations with certainty.

In contrast to retrospective parental interview studies, detailed analyses of family audio-video recordings demonstrated that cooing was already absent in 5/12 (42%) infants with classic RTT (Table 2; Einspieler et al., 2014a; Marschik et al., 2013b). Of course we need to be cautious when drawing such conclusions, because a spontaneous speech corpus never covers the whole set of vocalisations present. On the other hand, audio-video analyses have the advantage of focussing on the complexity, composition, acoustic properties, and quality of vocalisations. In this respect, it turned out that all twelve carefully documented infants later diagnosed with RTT and seven infants with its preserved speech variant (PSV) presented with abnormal vocalisations on inspiratory airstream (Marschik et al., 2009a, 2012a, 2013a, 2013b). From 3 months onwards, normal cooing was already interspersed with proto-vowel or proto-consonant alterations produced on ingressive airstream (Tables 2 and 3).

Babbling behaviour was documented in 35 trajectories of infants later diagnosed with classic RTT (five studies; Table 2) and in eleven trajectories of infants later diagnosed with PSV-RTT (three studies; Table 3). While 8/11 (73%) children with PSV-RTT reached babbling, the same is true of only 34% (12/35) of infants later diagnosed with classic RTT. However, even if the milestone of canonical babbling was reached, it was interspersed with atypical vocalisations of a breathy character and with pressed or high-pitched vocalisations (Marschik et al., 2013a, 2013b). These deviant characteristics were also accurately identified by 400 laypeople and professionals who listened to the respective audio recordings (Marschik et al., 2012a). Recently, an automatic acoustic signal level detector also achieved a recognition accuracy of 76.5% for vocalisations of 7- to 12-month-old infants later diagnosed with RTT (Pokorny et al., 2016). By means of extraction and analysis of signal level descriptors, atypicality was mainly associated with prosodic, spectral and voice quality features, as well as the auditory attribute 'timbre' (Pokorny et al., 2018).

3.5. A limited repertoire of gestures

Gestures facilitate the transition from the mere (though increasing) ability to comprehend language to the ability to produce it (e.g., Capone and McGregor, 2004; Iverson and Goldin-Meadow, 2005). At around 10 to 12 months, gestural development typically begins with deictic or prelinguistic gestures such as showing, giving, or pointing (Butterworth, 2003; Goodwyn and Acredolo, 1993). Children often use gestures like pointing to turn a single (proto)word into an utterance that conveys a sentence-like meaning. Hence, in typical development, the use of gestures is considered to be a forerunner of linguistic change, signaling that a child will soon be ready to produce multi-word utterances (Ozçalişkan and Goldin-Meadow, 2005). Representational or symbolic gestures are usually accompanied by vocalisations aimed to elicit parental responsiveness (Karmiloff and Karmiloff-Smith, 2009).

It has been hypothesised that an atypical speech-language development could be associated with a limited gestural repertoire in infants with RTT. In fact, Tams-Little and Holdgrafer (1996) found most of the gestures that typically appear at about the same time as proto-words to be missing in 17 children with a later diagnosis of RTT. Only one child exhibited giving, pointing, and showing gestures; the same child also attained her first words within the normal scope. Other studies documented an adequate age of onset for first gestures, although the repertoire remained limited (Bartl-Pokorny et al., 2013; Burford et al., 2003; Einspieler et al., 2014a, 2016; Marschik et al., 2012d). Seven children with a later diagnosis of RTT displayed 0–6 (median = 2) different gestures (Marschik et al., 2012d), most of which were deictic in character, e.g. when demonstrating an object or index finger pointing. The latter is already present during pregnancy as a motor pattern without communicative intent, and is consequently considered to be a crucial gesture in acquiring an age-adequate vocabulary, which also makes it a marker of delayed language acquisition (e.g., Butterworth, 2003; Capone and McGregor, 2004; Lüke et al., 2017; Marschik et al., 2013c). It is remarkable in this respect that index finger pointing was rare in females with RTT: it was only observed in 4/24 (17%) children (Marschik et al., 2012d, 2013a; Nomura and Segawa, 1990). Interestingly, females with PSV-RTT also had limited pointing abilities (Marschik et al., 2012c), which is in line with reports on limited pointing gestures in children with a later diagnosis of autism (Shumway and Wetherby, 2009).

Symbolic gestures such as nodding or shaking the head indicating "yes" or "no" were very rare (Tables 2 and 3; Bartl-Pokorny et al., 2013; Marschik et al., 2012d); it remains open whether these gestures actually conveyed a meaning or were perhaps even an atypical perseverative motor activity (Einspieler et al., 2016).

We finally conclude that the restricted repertoire of gestures and the delayed or absent response to interactive stimuli like being called by name (see 3.3.) mirror autistic symptoms. This view clearly refutes the assumption that autistic phenomena associated with RTT only appear later in development (Kaufmann et al., 2012; Marschik et al., 2012d, 2013b).

3.6. Can the first (proto)words be lost if they were never acquired in the first place?

At approximately 10–12 months of age, proto-words start to emerge. They have a consistent phonetical structure but are not necessarily consistent with the target language (Karmiloff and Karmiloff-Smith, 2009). Soon afterwards, typically developing children start to utter their first conventional words.

Retrospective parental reports on spoken words, especially as they are often based on diaries, are among the most reliable memories parents have of their child's first two years of life. It seems all the more remarkable that, according to parental questionnaires, 22 to 30% of more than 1900 females with RTT never spoke a word (Huppke et al., 2003; Fehr et al., 2011; Kerr et al., 2001; Neul et al., 2014; Urbanowicz et al., 2014). Three trajectory studies reviewed here revealed that 12/31 (39%) children never spoke a proto- or proper word (Table 2; Marschik et al., 2013a, 2013b: Witt-Engerström, 1992a). Another six children reportedly never spoke a proto-word from 9 to 12 months (Bartl-Pokorny et al., 2013), though obviously this may have changed after the first birthday. In a word, apparently every third to forth child never spoke a (proto)word. Do we therefore need to re-think one of the main inclusion criteria of RTT diagnosis (Neul et al., 2010)? Is it even possible to lose an acquired language if it hasn't been acquired by a considerable proportion of females with RTT?

Note that there are several careful documentations on children who have gone quiet at around 16–18 months, losing previously acquired speech (Kerr et al., 2006; Lee et al., 2013; Uchino et al., 2001). Those who had entered the stage of canonical babbling during their 7th month of age or had acquired some words early on were even able to speak two-word combinations before they stopped speaking (Marschik et al., 2012c; Uchino et al., 2001). The majority of the children, however, never reached the level of two-word combinations (Table 2). According to the natural history study, 82% of the individuals never acquired phrases (Neul et al., 2014).

Different results are available for 'atypical better' females with RTT (Neul et al., 2014): although only 6% never spoke single words, no less than 46% never reached the two-word-combination milestone. The few case reports (six studies) on PSV-RTT revealed that 10/14 children were able to speak single words (Table 3). However, these (proto)words were sometimes used repetitively and seemed to be perseverations of echolalic character rather than conventional words spoken in the target language (Marschik et al., 2014).

Considering all these data, we also need to be aware of the fact that speech-language development varies greatly and inter-individually. Bear in mind that, according to the Danish birth cohort study mentioned above, neither the majority of the cohort (of more than 60,000 toddlers) nor the six females with a later diagnosis of RTT were able to produce more than ten words by the age of 18 months (Marschik et al., 2018).

4. Towards a new era of studying early development in RTT

The manifestation of neurobehavioural regression is a crucial criterion for the diagnosis of RTT. Even if a *MECP2* mutation is identified but the child still shows no evidence of regression by the age of 5 years, the diagnosis of RTT should be questioned (Neul et al., 2010). Regression has so far been defined by the partial or complete loss of previously acquired skills such as purposeful hand use and speech-language abilities. But how are we to understand 'regression' in those 20–40 percent of children with RTT who never spoke a single word (see 3.5.)?

Basically, there seem to be two developmental trajectories characterising the early development of a child with a later diagnosis of classic RTT or its PSV: (i) certain milestones were not achieved age-adequately or not achieved at all; 'regression', here, might point to the fact that the lack of respective behavioural patterns appeared more and more worrisome with increasing age; and/or (ii) developmental milestones were achieved, and hence might deteriorate or even get lost during regression. Yet, if we look beyond the achieved/not achieved dichotomy, we might easily see qualitative deviances. Both the lack of achieved typical milestones and deviances from normal development (e.g. high pitched or inspiratory vocalisations) or first abnormal neurological patterns (e.g. hand stereotypies and abnormal general movements) mirror the impact of *MECP2* mutations on early brain development (Einspieler et al., 2005a; Feldman et al., 2016), although the process of how the cascade of gene expression changes to unfold and how network plasticity deteriorates is still unknown (e.g., Zoghbi, 2016). This lack of knowledge about the underlying neuropathological processes even increases when it comes to the puzzling phenomenon that some observed deviances (e.g., extended fingers barely manipulating objects, or abnormal vocalisations on inspiratory airstream) alter with perfectly normal behaviours such as pincer grasping or canonical babbling. Such an interspersed character of typical and atypical behaviours might also explain why parental memories and even developmental assessments (documented in medical reports) revealed an achievement of milestones: perhaps too little attention was paid to the quality of performance. We also need to be aware that subtle signs observable in video recordings may have been unrecognisable under usual clinical working conditions and interactions with families. With increasing age, however, subtle signs might become more and more prominent, and might thus mark the onset of regression. In other words, during the first year, expected and unexpected behaviours alternate; in the second year the unexpected behaviour increases to an extent where parents get more and more concerned (Budden, 2012; Einspieler et al., 2016). Consequently, by that time, the clinician might consider to discuss with the family the possibility of a serious neurological disorder instead of speculating on clinically vague and subtle earlier signs (Budden, 2012).

But how specific are these behavioural deviations to RTT? The lack of comparative studies on larger data sets still makes it impossible to say whether the absence of certain behaviours at a specific age band and/or, even more so, their abnormal quality is unique to RTT or is in fact shared by individuals with other developmental disorders. Recently, we compared findings on early vocalisations of infants later diagnosed with autism spectrum disorder, fragile X syndrome, and RTT (Roche et al., 2018), but did not get beyond listing features in the respective individuals. One of the main reasons for this is that family video material is not standardised. Even if the focus lies on a single behavioural pattern such as the child's reaction to his or her name being called, environmental situations and distractions videoed by parents are different for each individual (Zhang et al., 2018b).

Despite frequent suggestions that the findings of case reports should be verified in larger samples, the most comprehensive retrospective video analysis to date has been carried out in only 22 infants with a later diagnosis of RTT during their first 6 months of age (Einspieler et al., 2005a). This is regrettable, as well-organised international associations of parents and clinicians/researchers could no doubt collect sufficient audio/video material to enable a standardised approach based on comparison – material that would also be suitable for a finer-grained analysis and implementation of signal analytical approaches (e.g., Marschik et al., 2017).

Succeeding to delineate the earliest RTT-specific atypicalities will lead to an earlier diagnosis and hence to earlier general symptomatic, but also targeted intervention. Furthermore, it would enable an earlier support and specific counselling of the families, who still find it to be a major cause of distress that professionals didn't listen to their concerns (Bisgaard et al., 2015a; Burford et al., 2003; Marschik, 2014). If early clinical trials became available they might prove beneficial within a short space of time if treatment starts early (Zoghbi, 2016).

5. Conclusion

The challenging period of pre-regressional development in RTT should receive intensified attention in order for clinicians to delineate disorder-specific signs. We currently find ourselves in the – admittedly slow – transition phase from the original "asymptomatic-early-development assumption" to the (already accepted) "subtle-early-abnormality assumption" to the "RTT-specific-early-signs-paradigm". Future research efforts closely linked with parental and clinical resources need a more concerted strategy that goes beyond studies on small samples conducted so far. We are on the right track towards defining new and reliable neurofunctional markers for early detection of RTT.

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