Neuropsychology Review (2019) 29:465–483
https://doi.org/10.1007/s11065-019-09420-9

REVIEW

Caregiver- and Clinician-Reported Adaptive Functioning in Rett Syndrome: a Systematic Review and Evaluation of Measurement Strategies

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Received: 17 May 2018 / Accepted: 6 November 2019 / Published online: 20 November 2019

Abstract

Rett syndrome is the second most common cause of intellectual disability in females worldwide. The severity of many individuals' impairment limits the effectiveness of traditional assessment. However, clinician and parent reports of adaptive functioning may provide insight into these patients' abilities. This review aims to synthesize the current literature assessing adaptive functioning in Rett syndrome and evaluate existing measurement tools in this population. A search was conducted on PubMed using the search term "Rett syndrome." Studies that quantitatively assessed adaptive functioning outcomes in Rett syndrome with published and normed questionnaire measures were included. Twenty-three studies met inclusion criteria. Overall results indicate that the population of people with Rett syndrome is highly impaired, both in overall adaptive functioning as well as in specific subdomains (e.g., mobility, activities of daily living). Atypical Rett syndrome groups performed better on measures of adaptive functioning relative to patients with classic Rett syndrome. Our findings identified measurement weaknesses, as many of the studies found floor effects and therefore were unable to capture meaningful variability in outcomes. Individuals with Rett syndrome are highly reliant on caregivers due to disrupted adaptive functioning abilities. Optimizing measurement of adaptive skills in Rett syndrome will facilitate the quantification of meaningful change in skills and the identification of efficacious interventions aimed at improving outcomes and quality of life.

Keywords Activities of daily living · Intellectual disability · Outcome assessment (health care) · Review · Self-care · Mobility limitation

Rationale

Rett syndrome is a neurodevelopmental disorder that affects 1 in 10,000 live-born females worldwide with no specific racial or ethnic group selectivity (Neul et al., 2010). Despite its rarity and its naming just over 30 years ago, the corpus of literature on all aspects of Rett syndrome is large. Individuals with Rett syndrome are diagnosed after a period of apparently typical development followed by sudden loss of fine motor and language function within the first years of life, ultimately resulting in cognitive and functional impairment ranging from mild to severe (Tarquinio et al., 2015). Therefore, understanding the evolution of skills in everyday functioning is critical not only for understanding the presentation of Rett syndrome but also for monitoring the effectiveness of treatments. This study systematically reviews the extant research on adaptive functioning within the Rett syndrome population in order to summarize findings of these individuals' abilities and determine the suitability of presently available adaptive functioning measures.

Rett syndrome is caused by mutations in the X-linked gene, *MECP2*, which encodes methyl CpG binding protein 2 (Amir et al., 1999). Most "classic" or "typical" presentations of Rett syndrome involve some mutation of this protein. Atypical Rett syndrome cases show differences regarding timing of symptoms, seizure presentation, and speech capabilities and do not present with *MECP2* mutations as consistently (Pini et al., 2016). Recent research suggests that the specifics of the mutations on the gene (e.g., missense vs. nonsense) may impact the type and severity of an individual's deficits

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(Cuddapah et al., 2014; Percy, 2008). Clinically, individuals with Rett syndrome appear to develop normally until approximately 6 to 18 months of age (Tarquinio et al., 2015). These children may have already taken their first steps and begun to say words, but between 6 months and 18 months of age, their development slows and then regresses. Physical growth first slows with regard to head circumference, followed by weight and then height (Tarquinio et al., 2012). Gradual or sudden losses of speech and hand function are first noted, followed by gait disturbances and development of stereotyped hand-wringing movements (Anderson, Wong, Jacoby, Downs, & Leonard, 2014). Symptomatology is variable but often involves gastrointestinal problems, disorganized breathing, sleep disturbances, bruxism, scoliosis, and seizures (Anderson et al., 2014; Percy, 2016).

Formal clinical criteria for a Rett syndrome diagnosis has varied since its first explicit iteration in 1983 in which patients were required to present with 1) normal development during the first 7–18 months of life, 2) stagnation of development followed by deterioration to "dementia with autistic features" within 18 months, 3) loss of purposeful use of the hands, 4) ataxia of the trunk and possibly limbs, ataxic gait, and "acquired microcephaly," and 5) a later period of relatively stable mental status but with possible neurological abnormalities such as epilepsy (Hagberg, Aicardi, Dias, & Ramos, 1983). Updates in the diagnostic criteria have been made in the decades since (Hagberg, 2002; Hagberg, Goutières, Hanefeld, Rett, & Wilson, 1985; Trevathan & Moser, 1988), with the most recent update occurring in 2010 (Neul et al., 2010; see Table 1 for criteria). Presently, in order to receive a diagnosis of either classic or atypical Rett syndrome, the individual must demonstrate a period of regression followed by a period of stabilization. A classic Rett syndrome diagnosis requires that an individual meets all main diagnostic criteria and all exclusion criteria. Supportive criteria may be present, but none are required for the classic Rett syndrome diagnosis. A variant Rett syndrome diagnosis requires at least 2 of 4 main criteria and at least 5 of 11 supportive criteria to be present. Genetic testing is required to confirm the diagnosis (Neul et al., 2010). People with Rett syndrome historically have been misdiagnosed with autism spectrum disorder, cerebral palsy, or a non-specific developmental delay, but improvements in dissemination of information about the disorder have made diagnosis more accurate. Most children are now diagnosed with Rett syndrome by 2.7 years of age (Tarquinio et al., 2015).

Delineation of Rett syndrome into four stages across the lifespan was proposed by Hagberg and Witt-Engerström in the early literature (Hagberg & Witt-Engerstrom, 1986) and summarized most recently in 2002 (Hagberg, 2002). Stage I (early onset stagnation) is the initial onset of symptoms, occurring between 6 months and 1.5 years of age. Stage II (developmental regression) occurs between ages 1 and 4 and may range in duration from weeks to a year. Stage III (pseudostationary period) is marked by the conclusion of developmental regression and stability of symptoms. Some but not all individuals with Rett syndrome will progress into Stage IV (late motor deterioration) before the end of their life. See Table 2 for detailed symptoms by stage.

Neuropsychological evaluation is very challenging in this population because individuals rarely show sustained attention towards persons or objects, purposeful hand use, or expressive language (Hagberg et al., 1983; Neul et al., 2010). When present, expressive language is often limited to single words (Hagberg et al., 1983; Neul et al., 2010). Therefore, although Rett syndrome is generally regarded as the second most common cause for intellectual disability in girls following Down syndrome, intellectual abilities are difficult to measure in this population due to the demands of the requisite tests. A great deal of information on the abilities of patients with Rett syndrome is instead collected via informant report, often in the form of parent questionnaires or structured interviews in which the parent indicates which skills or impairments are present in his or her child.

Table 1 2010 Rett Syndrome Diagnostic Criteria (Neul et al., 2010)

Main Criteria
1. Partial or complete loss of acquired purposeful hand skills
2. Partial or complete loss of spoken language
3. Dyspraxic gait or inability to ambulate
4. Stereotypic hand movements: hand mouthing, hand wringing/clasping, hand clapping, or finger rubbing
Exclusion Criteria
1. Brain injury: peri- or postnatal trauma, neurometabolic disease, or severe infection involving neurological function
2. Grossly abnormal psychomotor development in first 6 months after birth
Supportive Criteria
1. Periodic breathing during wakefulness
2. Bruxism while awake
3. Altered sleep pattern
4. Abnormal muscle tone
5. Peripheral vasomotor disturbance
6. Scoliosis/kyphosis
7. Growth failure
8. Small cool/cold hands and/or feet
9. Inappropriate laughing or screaming spells
10. Delayed or diminished response to pain
11. Intense eye communication or "eye pointing"

Table 2 Clinical stages of Rett syndrome (Hagberg, 2002)

Stage	Description
Stage I:	Onset at 5–18 months of age
Early Onset Stagnation	Delay in developmental progress
	Development not yet significantly abnormal
	Early postural delay
	Dissociate development
	"Bottom-shuffling"
	Duration: weeks to months
Stage II:	Onset at 1–4 years of age
Developmental Regression	Loss of acquired skills/communication
	Examples: fine finger movement, babbling/words, active playing
	Mental deficiency
	Occasionally "in another world"
	Preserved eye contact
	Modest breathing problems
	Seizures in 15% of individuals
	Duration: weeks to 1 year
Stage III:	Onset at end of Stage II
Pseudostationary Period	Some restoration of communication
	Apparently preserved ambulation
	Slow neuromotor regression
	"Wake up" period
	Significant hand apraxia/dyspraxia
	Duration: years to decades
Stage IV:	Onset when Stage III ambulation ceases
Late Motor Regression	Complete dependency on wheelchair
	Wasting and distal distortion
	Division by subgroupings: A-previous walkers, now non-ambulatory; B-never ambulatory
	Duration: decades

One domain that is readily assessed by informant report, however, is that of adaptive functioning. Adaptive functions include personal functions of daily living, such as self-care and mobility, as well as interpersonal functions, such as communication and socialization (Sparrow, Cicchetti, & Balla, 2005). Significant deficits in adaptive functioning are now among the criteria required for a diagnosis of intellectual disability, and documented adaptive functioning deficits fall under one of five domains of development by which children may be eligible for intervention services within public school in the United States. Given the importance of independent living skills to families and health care providers, research has been devoted to studying adaptive functioning across the lifespan, from younger individuals with autism spectrum disorders (Mouga, Almeida, Cafe, Duque, & Oliveira, 2015) to older adults with Alzheimer's disease (Brigidi, Achenbach, Dumenci, & Newhouse, 2010). Likewise, some researchers have studied adaptive functioning outcomes in individuals with Rett syndrome.

Objectives

Since Rett syndrome inherently presents with a decline in motor and language skills as part of its diagnostic criteria, it is expected that individuals with Rett syndrome would demonstrate major challenges in adaptive functioning domains. As the aforementioned assessment challenges preclude many types of evaluations of intellectual ability in this population, adaptive functioning questionnaires and interviews may provide the greatest insight into these individuals' abilities and act as a broad predictor of other elements of cognitive and behavioral functioning. However, the question remains whether the commonly used adaptive functioning measures can sufficiently delineate among skill levels in very low-functioning populations such as Rett syndrome patients. Furthermore, if studies aim to assess changes over time, it is not yet clear whether traditional measures are sensitive to changes in this population. Thus, the aim of the present review is to systematically summarize the state of the quantitative literature on adaptive

functioning in Rett syndrome and evaluate the suitability of commonly used adaptive functioning measures for use with affected patients. This could help to identify strengths and weaknesses in the existent literature, identify future areas for research, and determine whether current measurement strategies are appropriate for use in intervention studies and other research in the future.

All studies include a sample from the population of people with Rett syndrome. Given the limited research on the topic, studies are included and described regardless of use of an intervention or comparison group. Adaptive functioning outcomes are assessed, and subdomain category data such as assessments of communication, self-care, or motor abilities are presented when available. Relationships between adaptive functioning and other cognitive, behavioral, and neurological outcomes are described. Both longitudinal and cross-sectional studies are included. Strengths and limitations across studies are also addressed, focusing on floor effects and overall utility in this vulnerable population, and recommendations for future research are elaborated.

Methods

The current review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Liberati et al., 2009). We conducted a systematic review as opposed to a meta-analysis due to substantial differences in measurement techniques across studies and differences in provided statistical outcome data. Although age-equivalent ability scores were provided in multiple studies, a meta-analysis of these findings was not conducted given the differences in actual age of participants and possibility of functional differences by age and stage.

Eligibility Criteria

Studies eligible for inclusion assessed adaptive functioning outcomes in multiple Rett syndrome patients. Measures used in these studies were published and normed and used quantitative approaches to assessing functioning. Qualitative studies were excluded due to the desire to assess the most psychometrically sound and easily administered measures. Studies assessed both parent and clinician report of patient functioning. Participants could be any age and in any stage of the syndrome.

Information Sources, Search Strategy, and Data Extraction

Included papers were published through September 16th, 2016. Eligibility assessment was performed according to a standardized procedure. Initially, titles and abstracts of all search results were reviewed to identify potentially eligible articles. Subsequently, potentially eligible articles were reviewed in full to determine whether they would be included. Information extracted from each study included: (1) characteristics of the participants (e.g., age and sex), (2) study design (e.g., longitudinal or cross sectional, whether there was a control group), (3) which measures were employed, (4) which informant completed the measure (i.e., parent, clinician, or both), and (5) quantitative results.

Risk of Bias and Analysis Plan

A rating system was created to guide discussion and provide a quantitative scale for interpreting strengths and limitations. This system was composed of five domains, including sample size, measurement validation, inclusion of a comparison group, inclusion of diagnostic criteria, and methodology (i.e., cross-sectional or longitudinal study). The decision for these categories was modeled after prior systematic reviews (Ailion, Hortman, & King, 2017; Wolfe, Madan-Swain, & Kana, 2012). A small sample size was less than 15 patients, a moderate sample size was 15–49 patients, and a large sample size was 50 or more patients. Table 3 includes sample demographic information, diagnostic criteria, and measures used, as well as the strengths and limitations of each paper included in this review. Given the variability in types of quantitative data reported, a systematic, narrative approach was used in this review.

Results

Study Selection

The initial search produced three thousand and sixty-four (3064) articles. See Fig. 1 for an overview of article screening and exclusion. Categories for exclusion included: articles not about Rett syndrome ($n = 152$), not in English ($n = 234$), animal models ($n = 335$), genetic or molecular ($n = 963$), surgical or neuroanatomical or laboratory findings or EEG ($n = 201$), abstract or symposium or commentary or bibliography ($n = 46$), epidemiological ($n = 13$), and theoretical ($n = 197$). The exclusion of these domains resulted in nine hundred and twenty-three (923) articles that in some capacity dealt with the behavioral aspects of Rett syndrome. The next round of exclusion criteria removed qualitative articles, review articles, and case studies ($n = 771$) to exclude papers that lacked a quantitative measure or only described cases. The final round of exclusion criteria focused on grouping the articles by the individual domains they assessed to be included in a future systematic review of Rett syndrome literature. These thirteen domains included motor, stereotypies, adaptive functioning,

Table 3 Methods employed across studies of adaptive outcomes in Rett syndrome

Reference	N	Age (Years) Mean (SD) Range	Design	Controls (Y/N)	Diagnostic Criteria	Measure Used; Informant	Main Results	Strengths	Limitations
Andrews et al. (2014)	214	17.6 (7.95) 3–34	Cross Sectional	N	Confirmed diagnosis with MECP2 or with Neul et al. (2010)	WeeFIM Type of activity based on Children's Assessment of Participation and Enjoyment model; Parent	Recreational, physical/skill-based and social activities were more frequently reported than self-improvement activities. Greater odds of participating in an activity if they had higher functional independence or if their mother had a university degree.	Large sample size. Used validated measure.	Limited in scope of adaptive outcomes, focused on mobility and participation in community activities. Did not include a comparison group.
Barnes et al. (2015)	74	5.35 (2.36) 2–11	Cross-sectional	N	Confirmed diagnosis with MECP2 mutation	VABS-II, assessed Communication, Daily Living Skills, Socialization and Motor Skills; Parent	Direct correlation between irritability subscale of the ADAMS and Vineland-II motor skills ($p = 0.04$)	Large sample size. Used a validated measure.	Study did not characterize adaptive behavior. Did not include a comparison group.
Byiers et al. (2014)	35	20.3 2–49	Cross-Sectional	N	No indication of diagnostic criteria	Inventory for Client and Agency Planning. Parent Stress Index, Short Form; Parent	Adaptive functioning skills did not relate to parental stress. However, 60% of parents reported stress in the clinical range of at least one subscale.	Moderate sample size. Used a validated measure.	No report of diagnostic criteria used for study. Study did not characterize adaptive behavior. Did not include a comparison group.
Cass et al. (2003)	87	$M_{2–4} = 3.17$ (0.67) $M_{5–9} = 7.5$ (1.833) $M_{10–19} = 13.67$ (2.167) $M_{20–44} = 27$ (7.5) 2.08–44.833	Cross-Sectional	N	76 met Hagberg 1988 criteria for classic RTT, 11 for atypical (Hagberg and Skjedal 1994).	Rated on the following: self-feeding, self-feeding with fork/-spoon, drinks using bottle or cup, dressing, toilet training; Parent & Clinician	No significant effect for age group, reflecting variation in dependency levels at each age group. Self- care scores were associated with hand use and communication scores ($r = .65$, $r = .48$ respectively).	Large sample size.	Used an experimental measure. A more quantitative measure may be more sensitive for determining whether regression is associated with age. Did not include a comparison group.
Cianfaglione et al. (2015)	92	20.5 4–47	Cross-Sectional	N	Hagberg criteria diagnostic from 2002	VABS subscales: Communication, Daily Living, Socialization	Significant associations between the simplified severity scores and all VABS domains except for socialization skills.	Large sample size. Used a validated measure.	Authors reported floor effects. 84.5% scored below a raw score of 20 on adaptive behavior composite and the remaining 13 between 20

Table 3 (continued)

Reference	N	Age (Years) Mean (SD) Range	Design	Controls (Y/N)	Diagnostic Criteria	Measure Used; Informant	Main Results	Strengths	Limitations
						and motor skills; Parent			and 34. Study did not include a comparison group.
Cianfaglione, Clarke, et al. (2016)	91	20.5 4–47	Longitudinal *VABS administered only at initial testing	N	71 were MECP2 positive. 20 were diagnosed by a clinician using Hagberg (Hagberg, 2002) criteria	VABS subscales: Communication, Daily Living, Socialization and Motor Skills; Parent	Correlations of age and VABS raw/age-equivalent scores showed significant small positive associations between age and daily living skills raw scores (r = 0.28), daily living skills age-equivalent scores (r = 0.29) and motor skills age-equivalent scores (r = 0.23).	Large sample size. Used a validated measure.	VABS was not administered at follow-up because scores were very low at initial testing. This indicates a floor effect. Study did not include a comparison group. Study did not characterize adaptive behavior.
Cianfaglione, Meek, et al. (2016)	10	15.7 5–32	Cross-Sectional	N	All genetically confirmed MECP2. 9 diagnoses with classic RTT and 1 diagnosed with atypical RTT.	VABS; Parent	Engagement in activity involving the use of hands was positively related to VABS motor skills age-equivalent score. Engagement that did not involve the use of hands was unrelated to VABS equivalent age score.	Study used a validated measure.	Sample size was small. All participants had milder severity scores; therefore, the generalizability is limited. Did not include a comparison group.
Colvin et al. (2003)	351	$M_{1976} = 18.4$ $M_{1994} = 4.8$ $M_{1997} = 2.8$	Cross-Sectional	N	Clinician diagnosis using 1988 Rett Syndrome Diagnostic Criteria	WeeFIM; Parent	Performance was greatest in mobility domain. WeeFIM scores were better for mild atypical group than the classic group.	Large sample size. Used a validated measure. Compared adaptive functioning in classic vs. atypical diagnoses.	At least one participant received the floor score (18) which indicates a floor effect. Did not include a comparison group.
Djukic, Rose, Jankowski, and Feldman (2014)	37	10.03 (7.72) 2–31	Cross-Sectional	Y, 34 Siblings 12 (6.48) 2–30	Neul et al. (2010)	VABS; Parent	VABS did not correlate with performance on eye tracking task.	Moderate sample size. Used a validated measure and a comparison group.	Possible floor effect due to VABS composite score.
Downs et al. (2008)	99	No mean reported 1.5–27.9	Cross-Sectional	N	No indication of diagnostic criteria	WeeFIM; Parent	Poor WeeFIM scores correlated with poorer general mobility	Large sample size. Used a	Did not define diagnostic criteria used. Study did not

Table 3 (continued)

Reference	N	Age (Years) Mean (SD) Range	Design	Controls (Y/N)	Diagnostic Criteria	Measure Used; Informant	Main Results	Strengths	Limitations
							and poorer complex motor skills.	validated measure.	include a comparison group.
Downs et al. (2010)	144	14.83 (7.83), 2–31	Cross-Sectional	N	No indication of diagnostic criteria	WeeFIM; Parent	Better hand function was associated with higher WeeFIM scores, even after controlilng for genotype and age.	Large sample. Study used several groups based on genotype.	Paper mentioned floor effect for the WeeFIM in their discussion.
Fabio et al. (2016)	34	No mean reported 5–36	Longitudinal *VABS administered only at initial testing	Y, Two separate groups of individu-als diag-nosed with RTT	RSDCWG 1988 criteria and genetic	VABS; Parent	The scores between both groups with RTT were the same.	Moderate sample size. Study used a comparison group and a validated measure.	VABS was not administered at follow-up session.
Fontanesi and Haas (1988)	18	No mean reported 2.5–23 years	Cross-sectional	N	1985 Hagberg and Witt-Engerst-röm Vienna Criteria	VABS A sub-sample completed the Bayley Adaptive Scales; Parent	Atypical RTT group had higher adaptive functioning than classical RTT. Age of onset was the best predictor of level of adaptive functioning.	Moderate sample size. Used a validated measure.	Study did not include a comparison group.
Giesbers et al. (2012)	63	M_{RTT}= 19.34 (11.39) 5.08–47.17 M_{ID}= 21.64 (11.54) 5.25–47.33	Cross-Sectional	Y, Other diagnosis (ID)	Genetic criteria confirmed in 79% of sample	Parental Questionnaire: Enuresis/ Urinary Incontinence and Vineland Screener 0–6 years; Parent	Adaptive functioning did not predict incontinence. No statistically significant differences were found in level of adaptive functioning between females with fecal incontinence and females without.	Large sample size. Study used a comparison group and a validated measure.	Researchers removed 2 RTT and 11 ID patients who had adaptive functioning of greater than 24 months for between-group analyses.
Hetzroni and Rubin (2006)	8	No mean reported 4–11	Cross-Sectional	N	Not specified	Adaptive Behavior Scale-School; Clinician	Rett syndrome individuals performed very poor to below average compared to individuals with intellectual disability.	Study used a validated measure.	Small sample size. Study did not define diagnostic criteria. Did not include a comparison group. Study did not characterize adaptive behavior.
Jian et al. (2007)	162	$M_{epilepsy}$ = 14 2.3–24.6 $M_{noepilepsy}$ = 10.1 1.9–24.5	Longitudinal *WeeFIM administered only at initial testing	N	Part of ARSD, 95% genetically confirmed	WeeFIM; No reporter specified	Poorer functional ability correlated with seizure rate.	Large sample size. Used a validated measure.	Study did not characterize adaptive behavior. Study did not include a comparison group.

Table 3 (continued)

Reference	N	Age (Years) Mean (SD) Range	Design	Controls (Y/N)	Diagnostic Criteria	Measure Used; Informant	Main Results	Strengths	Limitations
Kaufmann et al. (2012)	80	6 (3.4) 1.6–14.9	Cross-Sectional	N	Genetically confirmed	VABS and RSBQ; Parent	Greatest impairment was seen in socialization. The widest range was in communication. Increased age predicted poorer VABS composite and socialization. Overall adaptive function was not related to RSBQ scores.	Large sample size. Used a validated measure.	Did not include a comparison group. Excluded the motor and daily living skills scales because of impairment of RTT patients. Possible floor effect due to the raw score ranging down to 1.5.
Matson et al. (2008)	18	48.5 (9.4)	Cross-sectional	Y, Other diagnosis (ASD and ID)	DSM-IV classification and ICD-10 criteria	VABS; Parent	RTT group did significantly worse than ID controls on social skills assessment. RTT group did not do as poorly as autism on measures of social/autistic behaviors.	Moderate total sample size. Use of comparison groups with equal sample sizes ($n = 6$). Used a validated measure.	Small RTT subgroup.
Monteiro et al. (2014)	60	$M_{StageIII} = 9.14$ (5.84) 2.2–26.4 $M_{StageIV} = 12.45$ (6.17) 5.3–26.9	Cross-sectional	N	Used Larsson, Halbach diagnostic criteria, diagnosed by clinician	PEDI; Parent	51 participants out of 73 (71.2%) performed none of the self-care activities. Eight of the 59 mobility activities (13.5%) were not performed by any of the participants.	Large sample size. Used a validated measure. Compares RTT across two stages (III and IV).	Did not include a comparison group. Potential floor effects as performance was a score of zero in some areas.
Mount et al. (2003)	15	14	Cross-sectional	Y, Other diagnosis (ID)	Not specified	VABS Communication, Daily Living, Socialization, Motor, Composite	RS had lower age equivalent scores than SMR group on composite score, communication, daily living skills, and motor skills.	Used a control group for comparison.	Both groups were near least possible score. Only one RTT individual had a composite score above floor.
Perry et al. (1991)	28	2–19	Cross-sectional	N	RSDCWG 1988 criteria	VABS Communication, Daily Living and Socialization subscales; Parent	No relationships between age of onset and VABS social and communication domains. Chronological age correlated with daily living skills, but not communication and socialization.	Moderate sample size. Used a validated measure.	Authors report floor effects. None of the patients could complete the items requiring speech or fine motor skills. Study did not include a comparison group.
Schonewolf-Greulich et al. (2017)	27	40.7 30–60	Cross Sectional	N	Genetically confirmed	WeeFIM Self-Care and	RTT patients had difficulty performing most functional	Moderate sample size.	Authors report floor effects and longitudinal data

Table 3 (continued)

Reference	N	Age (Years) Mean (SD) Range	Design	Controls (Y/N)	Diagnostic Criteria	Measure Used; Informant	Main Results	Strengths	Limitations
					and clinical criteria: Neul et al. (2010)	Communication sub-scales, Clinical Severity Scale, Hoffer ambulation scale and RSGMS; Clinician	skills and are highly dependent on caregivers.	Used a validated measure.	would have improved generalizability. Study did not include a comparison group.
Wulffaert et al. (2009)	52	16.5 (11.8) 2.4–49.3	Cross Sectional	N	Genetically confirmed (from medical records)	Dutch Vineland Screener ($n = 32$) and VABS ($n = 20$); Parent	RTT patients had severe to profound intellectual disabilities and only 4 patients (8%) had a level of adaptive functioning higher than 12 months. These four had levels at 13, 16, 18 and 28 months.	Large sample size. Used a validated measure.	Authors report floor effects with some very low scores on VABS. Study did not include a comparison group.

Note: RTT = Rett syndrome, ID = Intellectual Disability, ASD = Autism Spectrum Disorder, WeeFIM = Functional Independence Measure for Children, VABS = Vineland Adaptive Behavioral Scale, PEDI = Pediatric Evaluation of Disability Inventory, RSBQ = Rett Syndrome Behavior Questionnaire, RSDCWG = Rett syndrome diagnosis criteria work group, ADAMS = Anxiety, Depression, and Mood Scale, RSGMS = Rett Syndrome Gross Motor Scale

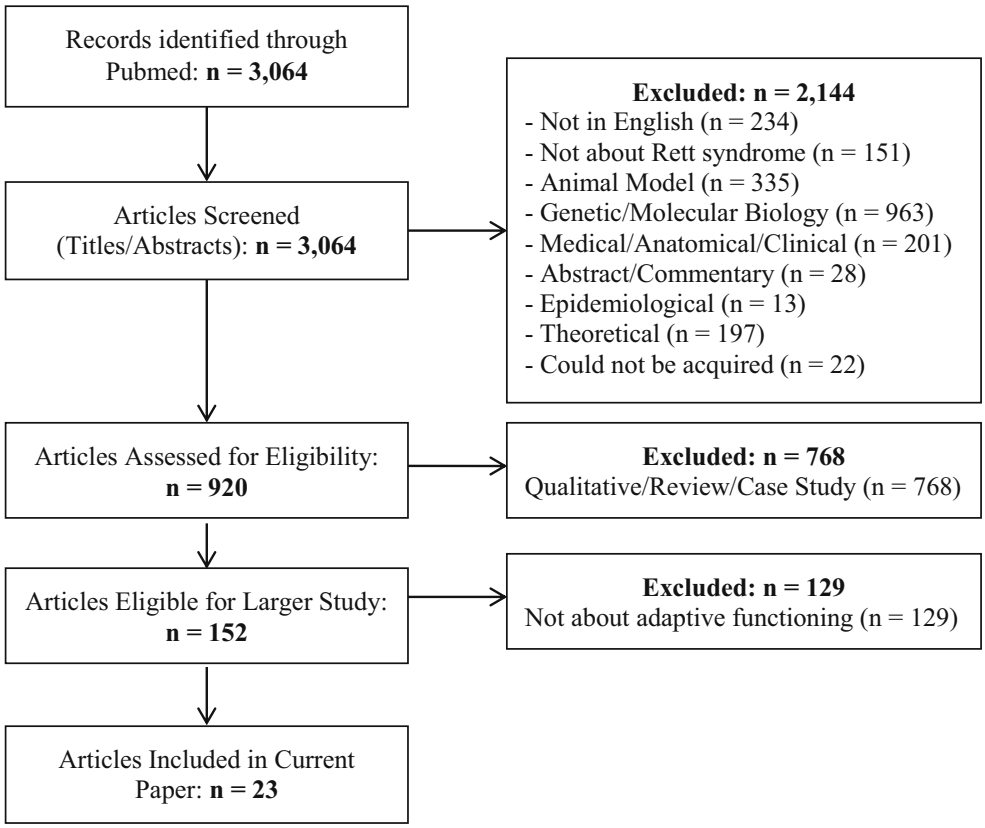

Fig. 1 Identification of included articles

cognition, language or speech or communication, psychosocial function, sleep, quality of life, pain, seizures, breathing, eating or nutrition, and scoliosis. Of the remaining 152 quantitative articles, 23 articles included measures of adaptive functioning in individuals with Rett syndrome and were therefore included in the current review.

Overall, these papers had a range of goals, with a minority (3/23) setting out specifically to study adaptive functioning as their main focus. The majority studied another aspect of Rett syndrome (e.g., seizures, general clinical severity) but controlled for adaptive functioning in their analyses. Nevertheless, all of the papers provided descriptive information on their adaptive functioning measurements, making each informative for the purposes of this review. Out of all measures collected across studies, 21/23 used parent report, 3/23 used clinician report, and one did not specify the informant. One study used parent and clinician report, while the remaining twenty-two papers used only one informant. Findings appeared consistent across informants. Studies originated in a variety of countries, most commonly the United States, the United Kingdom, and Australia. There were three longitudinal studies in this group, consisting of two descriptive studies of natural progression (Cianfaglione et al., 2016; Jian et al., 2007) and one intervention study (Fabio et al., 2016). However, none of these studies provided longitudinal data on adaptive functioning, thereby resulting in zero studies assessing adaptive functioning over time. In two cases, adaptive functioning measures were only given at one time point in accordance with the goals of the studies, and in the other case, the researchers cited a floor effect at time one as rationale for not re-administering their adaptive functioning assessment. However, a number of cross-sectional studies evaluated differences in adaptive functioning between different age groups, thereby providing some information on adaptive functioning skills across the lifespan.

Samples varied widely, with studies including an average of 78 girls with Rett syndrome, approximately (range: 8–351), and participant ages ranging from 1 to 60 years old. Almost half of our selected papers had fewer than 50 participants, which suggests the need for future studies with larger samples. Five of the 23 studies included control or comparison groups. These groups were predominantly comprised of other neurodevelopmental diagnoses (e.g., varying levels of intellectual disability, autism) but in other cases were healthy siblings or, in the study evaluating an intervention, a group of Rett syndrome patients who did not receive the intervention. Eighteen studies explicitly reported the method(s) through which they verified the Rett syndrome diagnosis, either noting that the participants had been evaluated with specific diagnostic criteria, had genetic confirmation, or both. The remaining five studies used less precise language surrounding the diagnostic procedures, indicating for example that the participants had "confirmed" cases of Rett syndrome (Byiers, Tervo, Feyma, & Symons, 2014; Downs et al., 2008; Downs et al.,

2010; Hetzroni & Rubin, 2006; Mount, Charman, Hastings, Reilly, & Cass, 2003).

Review of General Adaptive Functioning

Results of individual studies can be found in Table 4. Despite some variability, several noteworthy general trends in adaptive functioning abilities emerged. Among two studies that included an overall assessment of clinical severity, clinical severity was associated with poorer adaptive functioning (Cianfaglione et al., 2015; Kaufmann et al., 2012). This is perhaps unsurprising, given that existing clinical severity scales assess the state of basic functions that, in their absence, would make it very difficult to engage in independent adaptive functioning (e.g., ability to stand on own, purposeful hand movements).

Secondly, while none of the papers reviewed studied adaptive functioning longitudinally, some studies recruited participants of different ages and compared characteristics of Rett syndrome patients across the lifespan. They suggest that changes in adaptive functioning remain relatively stable over time (Cass et al., 2003; Cianfaglione, Clarke, et al., 2016). However, small and statistically nonsignificant changes in adaptive functioning have also been described. For example, both increases and decreases in motor functioning have been found during different developmental periods, as discussed below. Therefore, it would appear difficult to draw broad conclusions about changes in adaptive functioning in general based on the existing literature. An important consideration in interpreting the results of studies of Rett syndrome is that these samples are all comprised of individuals who were older than when one would expect to see rapid regression (i.e., Stage II). Thus, naturally occurring changes in functioning are not expected to be large. However, a failure to detect any change whatsoever may be indicative of inadequate sample sizes or measurement techniques.

Out of studies that used control groups, the general finding was that Rett syndrome patients experience poorer adaptive functioning outcomes than other individuals with severe intellectual disability (Matson, Dempsey, & Wilkins, 2008; Mount et al., 2003). However, Matson et al. (2008) noted that girls with Rett syndrome in their sample did not differ from their autism control group on any of the Vineland Adaptive Behavior Scale subscales. The Vineland is a widely used questionnaire measure that assesses adaptive functioning across several domains and also provides a general composite scale (Sparrow, Cicchetti, & Saulnier, 2016). When comparing amongst groups of Rett syndrome patients, a number of papers concluded that groups with atypical Rett syndrome fared better on measures of adaptive functioning than classic Rett syndrome groups and that an effect emerged for age of onset, such that individuals with later onset exhibited better outcomes (Colvin et al., 2003; Fontanesi & Haas, 1988; Perry, Sarlo-McGarvey, & Haddad, 1991). This is potentially because individuals with later onset generally would have had the opportunity to acquire more functional skills before regression began.

Taken together, the studies included in this review pointed to a high degree of reliance on caregivers due to low levels of general adaptive functioning (Cass et al., 2003; Schonewolf-Greulich, Stahlhut, Larsen, Syhler, & Bisgaard, 2017). The mean age equivalence of the overall composite scores for all of the studies that reported descriptive data on the Vineland were below 12.4 months, and standard deviations were between 3 and 5 months, suggesting that most of the individuals in these samples were functioning at a level below 2 years of age. Mean age-equivalents for each of the domains on the Vineland were at or below 12 months across studies. Similarly, mean raw scores on the Functional Independence Measure for Children (WeeFIM) overall were between 29 and 31.6 for all studies that used this measure (Msall et al., 1994). The range of scores possible on the WeeFIM are 18 through 126, indicating that individuals with Rett syndrome on average are highly dependent and require maximal assistance from caregivers. In fact, one study noted that only four of the 52 participants were at age-equivalent levels of 12 months or higher (Wulffaert, Van Berckelaer-Onnes, & Scholte, 2009). In the following sections, more specific findings pertaining to individual domains of adaptive functioning are reviewed.

Review of Subdomains

Several of the studies included in this review broke down adaptive functioning into subscales in order to provide more nuanced descriptions of abilities in patients with Rett syndrome. The most commonly studied subdomains of adaptive functioning can be described as mobility, socialization, communication, and activities of daily living. Therefore, these four categories of adaptive functioning are reviewed below. In spite of the previously discussed general trends in adaptive functioning, the specific domains in which patients are most impaired varied by study. Still, these studies contain valuable information regarding more specific skill sets and their performance in the Rett syndrome population.

Mobility

Adaptive mobility is an individual's ability to move their body to accomplish day to day tasks, for example, moving about a room or walking up stairs. Although adaptive mobility has been described as less impaired compared to other domains like communication, socialization, and activities of daily living (Colvin et al., 2003; Monteiro et al., 2014), individuals with Rett syndrome are still often quite impaired when it comes to mobility. Monteiro and colleagues used the Pediatric Evaluation of Disability Inventory (PEDI) and found

Table 4 Characterization of adaptive outcomes across studies of patients with Rett syndrome

Reference	Sample Age (Years)	Measure	Subdomain	Scores: M (SD), Range		
				Raw	Standard	Age-Equivalent (mo.)
Andrews et al. (2014)	17.6 (7.95), 3–34	WeeFIM	Composite	29.4 (14.4)		
Barnes et al. (2015)	5.35 (2.36), 2–11	Vineland-II		No quantitative descriptives reported		
Byiers et al. (2014)	20.3, 2–49	Inventory for Client and Agency Planning		No quantitative descriptives reported		
Cass et al. (2003)	2–44	Experimental Assessment Battery	N/A	Behavioral counts reported, no summary statistics		
Cianfaglione et al. (2015)	20.5, 4–47	Vineland	Composite			10.5 (3.50), 4–23
			Communication			9.90 (4.67), 1–34
			ADLs			12.7 (3.91), 1–23
			Socialization			9.00 (4.53), 1–23
			Mobility			5.50 (5.52), 1–23
Cianfaglione, Clarke, et al. (2016)	20.5, 4–47	Vineland	N/A	No quantitative descriptives reported		
Cianfaglione, Meek, et al. (2016)	15.7, 5–32	Vineland	Composite			Median = 11, 11–15
Colvin et al. (2003)	M_{1976} = 18.4 M_{1994} = 4.8 M_{1997} = 2.8	WeeFIM	Composite	29.0 (11.5)		
Djukic et al. (2014)	7.72, 2–31	Vineland	Composite		45.9 (12.5), 21–73	
Downs et al. (2008)	Median: 14.1, 1.5–27.9	WeeFIM	Composite	29.02		
Downs et al. (2010)	14.1 (7.1), 2–31	WeeFIM	Composite	31.6 (11.6), 18–85		
Fabio et al. (2016)	5–36	Vineland	Communication	17.23 (4.45)		
			ADLs	16.98 (4.11)		
			Socialization	28.00 (6.49)		
			Mobility	15.86 (8.58)		
Fontanesi and Haas (1988)	2.5–23	Vineland		Reported in graph		
Giesbers et al. (2012)	19.3 (11.4), 5–47	Vineland Screener	Composite			9.0 (8.0), 2–38
Hetzroni et al. (2006)	4–11	Adaptive Behavior Scale - School	N/A	No quantitative descriptives reported		
Jian et al. (2007)	14, 2–24	WeeFIM	N/A	No quantitative descriptives reported		
Kaufmann et al. (2012)	6.0 (3.4), 1–14	Vineland	Communication	21.5 (13.7)		
			Socialization	19.7 (12.2)		
Matson et al. (2008)	48.5 (9.4)	Vineland	Communication	17.33		
			ADLs	35.33		
			Socialization	20.33		
Monteiro et al. (2014)	2.2–26.9	Pediatric Evaluation of Disability Inventory	ADLs	Stage III: 24.12 Stage IV: 18.36		
			Socialization	Stage III: 17.72 Stage IV: 12.14		
			Mobility	Stage III: 37.22		

Table 4 (continued)

Reference	Sample Age (Years)	Measure	Subdomain	Scores: M (SD), Range		
				Raw	Standard	Age-Equivalent (mo.)
				Stage IV: 14.64		
Mount et al. (2003)	13.6 (2.1), 11–18	Vineland	Composite			12.4 (2.2)
			ADLs			13.4 (2.0)
			Communication			12.8 (2.5)
			Socialization			10.9 (3.3)
			Mobility			9.30 (4.9)
Perry et al. (1991)	9.4, 2–19	Vineland	ADLs			16.9 (7.3), 4–34
			Communication			17.4 (5.5), 5–28
			Socialization			25.0 (4.9), 14–36
Schonewolf-Greulich et al. (2017)	40.7, 30–60	WeeFIM	ADLs	8.44 (2.79), 6–15		
			Communication	3.67 (1.47), 2–7		
Wulffaert et al. (2009)	16.5 (11.8), 2.4–49.3	Vineland Screener	Composite			7.6 (4.4)

ADLs = Activities of Daily Living, Vineland = Vineland Adaptive Behavior Scales, WeeFIM = Functional Independence Measure for Children, mo. = Months

Total Raw Score Ranges:

Vineland: Communication = 0–126, ADLs = 0–198, Socialization = 0–128, Mobility = 0–51

Vineland-II: Communication = 0–198, ADLs = 0–218, Socialization = 0–198, Mobility = 0–152

WeeFIM = 18–126

that none of their 60 participants had ever demonstrated an ability to complete 13.5% of the mobility items on the questionnaire (Hayley, Coster, Ludlow, Haltiwanger, & Andrellos, 1992; Monteiro et al., 2014). Examples of items on the mobility activities subscale of the PEDI include "sits if supported with equipment," "moves within a room, but with difficulty," and "scoots or crawls up partial flight of stairs." In general, mobility seems to be quite impaired, with studies reporting average age equivalents of 9.3 months and 5.5 months (Cianfaglione et al., 2015; Mount et al., 2003). However, studies also suggest that substantial variability exists in this domain of functioning. A study of 214 individuals with Rett syndrome by Andrews et al. (2014) found that on a measure of walking, 38.3% of participants were only mildly restricted, while 43% were only able to support their own weight briefly or needed full assistance, therefore demonstrating a wide range of abilities. Another large study by Colvin et al. (2003) examined 351 participants and concluded that 39% were characterized as "mobile," 12% could manage stairs independently, and 22% could get in and out of a chair alone or with assistance. Finally, one Danish study found that 67% of individuals could move from standing to sitting without support, further supporting that functional mobility might be a relative strength for Rett syndrome patients (Schonewolf-Greulich et al., 2017). There have also been estimations of change over time based on comparing cohorts, which have led to the suggestion that improvements in mobility are common in adolescence, followed by declines through adulthood (Cass et al., 2003). This is consistent with the observations made in establishing the stages of Rett syndrome, where Stage IV is characterized by motor regression (Hagberg & Witt-Engerstrom, 1986). Other studies have found significant correlations between adaptive motor function (mobility and hand function) and adaptive functioning overall assessed by the WeeFIM (Downs et al., 2008; Downs et al., 2010). Some studies have found significant correlations between motor function and general community participation as well as mood symptoms, implying that poorer adaptive motor skills can have wide-ranging negative impacts on quality of life (Barnes et al., 2015; Cianfaglione et al., 2016).

Socialization (Interpersonal Relationships, Play and Leisure, Coping Skills)

Adaptive socialization includes issues such as interpersonal relationships, play and leisure, and coping skills. This was the least studied domain of adaptive functioning out of all the papers reviewed, with only three papers providing ratings.

As such, it is difficult to draw broad conclusions about the state of adaptive socialization in this population. One paper noted that socialization was a relative strength compared to other domains of adaptive functioning assessed. However, this paper only assessed adaptive functioning as a potential confound for its main analyses and had the smallest sample size of the three papers, which are both factors to consider when interpreting these results (Fabio et al., 2016). In contrast, the remaining two papers reported that socialization was the most impaired form of adaptive functioning that they assessed (Kaufmann et al., 2012; Monteiro et al., 2014). Specifically, Kaufmann and colleagues reported that increased clinical severity and increased age were both related to increased impairment in adaptive socialization. Monteiro and colleagues reported that 77% of the socialization functions on the PEDI were not performed by any of their participants. Examples of items in the social function activities subscale are "notices the presence of other children and may vocalize or gesture," "uses gestures with clear meaning," and "shows awareness and interested in others." Three studies provided age equivalent score for adaptive social function, which found mean scores of 9, 10, and 25 months (Cianfaglione et al., 2015; Mount et al., 2003; Perry et al., 1991). These scores indicate very impaired functioning based on the age of the samples. Given the small sample of papers available and the variability within them, it is imperative that more research be done on this area of adaptive functioning before definitive conclusions are made.

Communication (Receptive, Expressive, Written)

Adaptive communication is the ability to communicate needs and desires. This was also a minimally studied domain of adaptive function. We were able to identify only four papers in our sample that reported on these skills, one of which reported that this domain comprised the widest range of abilities of the adaptive functioning domains studied (Kaufmann et al., 2012). Specifically, the raw scores from the Vineland communication scale in this study ranged from 1.5 to 73.7, with a standard deviation of 13.7. Mount et al. (2003) reported that their Rett syndrome sample had significantly lower age-equivalent communication scores than the severe intellectual disability comparison group. When examining communication in a more nuanced manner with the WeeFIM, one study found that comprehension was better than expressive language amongst a group of older women with Rett syndrome (Schonewolf-Greulich et al., 2017). Despite this relative comparison, both scores were extremely low, with means of 2.11 and 1.56, respectively. This yielded a total average communication score of 3.67, with 14 being the highest possible score. The authors characterized these results as constituting a need for "maximal assistance to express needs and feelings" and highlighted communication as an important area of further study for this population. Finally, the last study that evaluated communication in this sample characterized communication skills as limited. However, the authors found little evidence of deterioration over time based on different aged cohorts (Cass et al., 2003).

Activities of Daily Living (ADLs)

Activities of daily living (ADLs) include a variety of self-care activities such as eating, bathing, and dressing. Nine of the studies in our review reported ADLs. Overall, the most robust finding was that later age of onset was associated with better ADL outcomes (Cianfaglione et al., 2015; Fontanesi & Haas, 1988; Perry et al., 1991). Additionally, ADL outcomes were positively associated with age overall, suggesting marginal improvement over time (Cianfaglione, Clarke, et al., 2016; Perry et al., 1991). One exception was that Cass and colleagues found slightly lower feeding ability ratings for their older age groups, suggesting a possible decline over time in feeding skills. However, they noted that dressing and toilet training did not vary by age (Cass et al., 2003). These authors also found that self-care skills were positively related to hand use, communication, and mobility in their sample. Overall, most studies characterized ADLs in Rett syndrome as extremely limited, with multiple studies describing their participants as substantially, if not completely, reliant on caregivers (Cass et al., 2003; Colvin et al., 2003). Rett syndrome patients were found to have lower age-equivalent scores for ADLs than a severe intellectual disability comparison group, and one study found that 71.2% of the ADLs assessed on the PEDI were never performed by any participants in their study (Monteiro et al., 2014; Mount et al., 2003). Examples of these activities included "keeps head still while hair is combed," "eats foods ground/granulated," and "indicates when wetting diapers or pants." Finally, one study that evaluated incontinence in Rett syndrome found no association between incontinence and overall adaptive functioning, suggesting that this is a widespread problem that occurs despite variability in adaptive functioning outcomes (Giesbers et al., 2012).

Review of Measurement Strategies

Overall, there were 11 unique measures of adaptive functioning amongst all of the papers in this review, used for a total of 26 measurements. The most commonly used measures of adaptive functioning in our sample of papers were the Vineland and the WeeFIM. Twelve of the reviewed papers utilized the Vineland or Vineland-II and six used the WeeFIM. These are commonly used measures that have been psychometrically validated and published for use in a variety of populations (Msall et al., 1994; Sparrow et al., 2005). Overall, 22 of the 23 papers in our review used published, psychometrically validated measures of adaptive functioning,

and one used an experimental measure, a study-specific schedule for adaptive function assessment, completed using clinical evaluations and chart reviews. For the study-specific instrument, a moderate amount of detail about the types of items included was described in the manuscript (Cass et al., 2003). Twenty-three of the overall 26 measurements were reported independently by parents or caregivers, while there were 4 clinician-rated assessments; one of the measures was completed by both parents and clinicians.

Unfortunately, given that none of these studies assessed adaptive functioning at more than one time point, we are unable to report on the ability of these measures to detect change over time in the Rett syndrome population. However, studies that assessed functioning in a variety of age groups and compared them generally yielded few differences. Five studies mentioned the possibility of the presence of a floor effect for the measures they used, and we were able to identify the possibility of floor effects in an additional four studies based on the descriptive statistics reported. Authors who reported potential floor effects reported them for the Vineland and WeeFIM, for example, in one study, there was at least one participant who received a raw score of 18, which is the lowest possible score on the WeeFIM (Downs et al., 2010). These findings raise important issues for measurement strategies in this population.

Discussion

Summary of Evidence

Results from research studies examining adaptive functioning outcomes in patients with Rett syndrome consistently suggested very limited adaptive functioning skills overall and in each of the specific domains that were examined. The mean age equivalence of the overall composite scores for all of the studies that reported descriptive data on the Vineland were below 12.4 months, and standard deviations were between 3 and 5 months, suggesting that most of the individuals in their sample were functioning at a level below 2 years of age. Mean age-equivalents for each of the domains on the Vineland were at or below 12 months across studies. Similarly, mean raw scores on the WeeFIM overall were between 29 and 31.6 for all studies reporting descriptive quantitative data on the WeeFIM. As noted, the range of scores possible on the WeeFIM are 18 through 126, indicating that individuals with Rett syndrome on average are highly dependent and require maximal assistance from caregivers. Several studies failed to find significant relationships between age and adaptive functioning outcomes in samples with very broad age ranges (e.g., toddler to 40s), suggesting that patients with Rett syndrome remain within this very limited range of functioning overall and across motor functioning, socialization, communication, and daily living skill domains as they age.

Researchers also found relationships between adaptive functioning domains and other variables. For instance, motor functioning outcomes have been associated with community participation, mood, mobility, and hand function, suggesting that motor function has far-reaching consequences for other domains. Findings across studies also indicated that activities of daily living are extremely limited, with many patients requiring a maximum level of support from caregivers to carry out activities such as eating, bathing, toileting, and dressing. Research also suggested poor communication overall but indicated that receptive language skills may be higher than expressive language skills.

Studies exploring the relationships between patient clinical characteristics and adaptive functioning skills suggested that increased clinical severity is associated with poorer overall adaptive functioning. Individuals diagnosed with the atypical form of Rett syndrome, that is, those who do not meet all four main criteria of loss of purposeful hand skills, loss of language skills, dyspraxic gait, and stereotypical hand movements, tend to experience better adaptive functioning outcomes compared to individuals with the classic Rett syndrome. Further, later age of onset was generally associated with higher adaptive functioning skills. It is important to note that these findings are suggestive rather than conclusive, given that there are still relatively few studies that examine adaptive functioning outcomes by clinical group; there is a clear need for more detailed research studies on adaptive function and Rett syndrome diagnostic presentation.

Limitations

There were some inconsistencies across studies regarding which domain was most impaired, which may be a direct reflection of the small convenience samples in many of the studies as well as the wide variability in outcomes inherent in this clinical group. The vast majority of studies in this population use small samples, limiting statistical power and assessment validity. This is understandable, given the rarity of the syndrome, but this highlights the need for more multi-site studies in the future. There were also mixed findings regarding whether adaptive functioning skills change differs in differently aged cohorts. None of the research studies administered an adaptive functioning measure at two different time points, all instead used cross-sectional methods to investigate the relationships between age and adaptive functioning. Results from these types of studies were inconsistent, with some studies concluding that adaptive functioning was statistically unrelated to age and thus remained stable over time, and other studies providing evidence for decline in socialization with increased age, decline in motor functioning with increased age, and marginal improvements in activities of daily living with

increased age. Despite these descriptions, patients with Rett syndrome were consistently below peer skill level whether examining scaled scores, raw scores or age-equivalents.

These mixed findings may be a product of specific samples and methodological choices by researchers. For example, participants from these studies had large age ranges (e.g., age 2 through 49), and different researchers used varying age "bands" to categorize their patients into different age groups. These choices may have resulted in varying distributions of individuals in Stages I through IV of the disorder in different age bands. For instance, a study that separates individuals in Stage III versus Stage IV in different age bands may be better able to identify differences in motor functioning across age groups when compared to another study sample that includes both stages into the same age band. Similarly, despite the fact that many studies in the Rett literature use the staging system to categorize participants, there is a good deal of overlap in outcomes and abilities between stages themselves. This likely highlights a failure to fully capture the nuances of outcomes over the course of this syndrome. Future work should aim to evaluate the utility of this staging system and whether its continued use is warranted.

The lack of conclusive findings may also be due in part to the measurement instruments used to assess adaptive functioning being insensitive to the types of changes that are meaningful for patients with Rett syndrome and their families. Many studies that provided the range of standard scores and raw scores on adaptive functioning measures indicated that the lowest possible score was often achieved by at least one person in their sample. This raises the concern that these measures were unable to accurately characterize individuals performing at the lower end of functioning and thus were susceptible to floor effects.

Several studies transformed raw scores to age-equivalents or developmental age in an attempt to avoid the problems associated with using standard scores that are at floor level. However, issues with floor effects are also evident when using age-equivalent scores. For instance, on the socialization domain on the Vineland Adaptive Behavior Scales, individuals scoring between 0 and 9 raw points all receive the same lowest age-equivalent (i.e., below 0 years, 1 month). The age-equivalent score fails to distinguish between a patient who does not respond at all to their caregiver and another patient who shows affection to and reaches for another person. This effectively reduces the variability between these patients into a single score and removes the possibility of finding statistical differences where there might be clinically meaningful differences. For instance, although the latter case still qualifies as extremely impaired when using qualitative descriptors that compare performance to typically developing individuals, moving from one skill level to another within the same age-equivalent may nevertheless represent meaningful changes for patients and their families.

Overall, studies that experience floor effects on measures such as the Vineland and WeeFIM may also be underestimating the level of change that occurs with age in this group. Notably, longitudinal studies employing measures with floor effects may be unable to address the question of whether there are changes in adaptive functioning skills as patients with Rett syndrome age. Reduced variability at the lower range of functioning due to floor effects may also explain why other studies failed to find significant relationships between adaptive functioning and other clinical characteristics, skills, and other symptoms. It is difficult to find relationships between variables when variance is constrained in one variable.

In addition to the established issues with floor effects on the Vineland, it should also be noted that almost all of the studies utilizing the Vineland used the first edition of the measure, which was published, validated, and normed in 1984. Although many of these studies used archival data obtained from prior decades or used the first edition of the Vineland to maintain continuity in active research studies, there are important issues to consider when using and interpreting older measures and older normative data in research studies. For instance, older versions of the measure include skills that are less relevant now (e.g., using pay phones) and exclude skills that reflect a person's ability to use the technology that has rapidly transformed the way that people connect, socialize and engage with others and their communities. As such, continuing to use older versions of adaptive functioning measures may result in invalid characterizations of modern adaptive functioning skills. The creators of the Vineland have acknowledged these changes and recently released the third edition of the Vineland, which has revised many items and included new items to reflect the increased use of technology in everyday life (Sparrow et al., 2016). There are also established issues with using older norms, such as cohort effects and Flynn effects that may lead to spurious over- or underestimates in scores on adaptive functioning measures that do not reflect the underlying construct (Flynn, 1987).

Given these limitations in the measurement instruments in these studies, ongoing studies that investigate adaptive functioning in patients with Rett syndrome should consider using updated measures such as the third edition of the Vineland, which includes more items on the lower end of functioning. If this is not possible, researchers are encouraged to explicitly consider the potential impact of these limitations on their findings. These studies should report the ranges in addition to means and standard deviations when reporting descriptive data as well as the number of individuals who scored the lowest score on the measure to inform their readers about potential floor effects in their sample. Studies should acknowledge exactly how the floor effects or limited range could be impacting their findings or lack thereof. They should also indicate when they are using age-equivalent scores, raw scores, or standard

scores when running their analyses. This is especially important for studies that attempt to investigate the relationships between age and adaptive functioning using age-corrected standard scores. A statistically significant relationship between increasing age and decreasing standard scores in cross-sectional studies may reflect actual decline and loss of previously acquired skills or may simply reflect that patients are not acquiring skills at the same rate as their same-aged peers. Researchers should also consider using domain and subdomain scores in their analyses. The wide variability in outcomes across the different domains may render the overall summary adaptive functioning score relatively uninformative for this population.

Although several research studies have supported the use of the Vineland and WeeFIM in various clinical groups, the psychometric properties of these measures have yet to be established in patients with Rett syndrome. Indeed, generalizing the use of these measures to patients with Rett syndrome may be problematic since the studies reviewed here suggest that these measures have limited use in appropriately describing adaptive functioning skills and assessing change in Rett syndrome. Based on these limitations, it will be crucial to develop and validate a measure that specifically captures the skills relevant for patients with Rett syndrome and considers common medical comorbidities that may pose limitations or change how adaptive functioning skills manifest in daily life. In order to avoid floor effects, such a measure should include specific items that capture subtle differences occurring at the lower end of functioning. For instance, instead of considering toileting an all-or-none skill, the measure could include a series of items that break down the skill and assess the degree to which patients with Rett syndrome are able to assist with toileting. Given that mobility is often an issue for patients, the measure could include specific items that assess the patient's ability to ambulate with the use of a wheelchair or assess the temporal extent to which patients are able to sit unaided. Further, given that loss of expressive language abilities is a core feature of Rett syndrome, items should include other means to assess the ways that patients with Rett syndrome communicate with the people around them (e.g., eye gaze, communication devices, gestures). An important consideration in the development of such a measure is the wide variability in this group. For instance, the measure should be flexible enough to include items that assess different skill levels related to eating but also consider the fact that a portion of patients with Rett syndrome use a gastrostomy tube exclusively for nutritional purposes and do not have the opportunity to display eating skills.

With respect to the current review, limitations include the restriction to only including studies that used published and normed quantitative measures of adaptive functioning. While this was a valuable way to evaluate the most psychometrically sound measures that have been used in this population, there is likely other information to be gleaned from studies using experimental measures and qualitative rating systems. While these studies were outside the scope of this review, it could be a fruitful area of inquiry for future projects.

Conclusions

Overall, the current literature suggests very limited adaptive functioning skills in patients with Rett syndrome and that these patients require maximal to total assistance. These studies also highlight that the measures commonly used to assess adaptive functioning skills are not necessarily capable of fully characterizing these skills due to limitations in discrimination and validity in assessing this population. Given the rapid rate of medical advances and genetic research in this population over the past several decades, it is imperative to obtain an accurate characterization of adaptive functioning skills in individuals with Rett syndrome and to be able to assess improvements that may occur with different pharmacological or other interventions. Future directions in this area include development and use of measures that allow for greater elaboration for detailing the lower end of the skill range so that clinically meaningful changes in patients with Rett syndrome can be assessed. Optimizing measurement of adaptive skills in Rett syndrome will facilitate the identification of efficacious interventions aimed at improving outcomes and quality of life.

Acknowledgments We thank the students in Dr. King's Developmental Neuropsychology Across the Lifespan (DNP-ATL) Laboratory who assisted with acquiring and organizing articles for the systematic research review. Research reported in this publication was supported by Georgia State University initiatives which provided DNP-ATL graduate student fellowships: Brains & Behavior (S.D.N., M.E.F., E.S.S.), and 2CI Neurogenomics (R.K.).

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