



## REVIEW

# Non-medical interventions for individuals with Rett syndrome: A systematic review

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**Abstract**

**Background:** Research into Rett syndrome has included various medical interventions. Non-medical interventions are relatively under-researched. Recent technological communication intervention advances have contributed to the evidence base in Rett syndrome.

**Method:** The Embase, PsycINFO and MEDLINE were systematically searched for peer-reviewed papers describing non-medical interventions for Rett syndrome. All identified papers were evaluated for methodological quality.

**Results:** Thirteen studies of adequate methodological quality were reviewed (across  $N = 60$  participants). Interventions were primarily communication interventions including music, assistive technology, augmentative and alternative communication strategies, attentional training and cognitive rehabilitation training. All studies reported positive outcomes across communication, quality of life, brain stem activity, physical fitness and a reduction in stereotyped behaviour. However, methodological challenges to generalizability, standardization, lack of follow-up and/or small-N samples were common.

**Conclusions:** The review highlights the paucity of high-quality research. Future research is needed to build on current research and improve validity and generalizability of interventions.

**KEYWORDS**

non-medical interventions, Rett syndrome, systematic review

## 1 | INTRODUCTION

Rett syndrome (RTT) is a rare neurodevelopmental disorder occurring in one in every 10,000 live births. It is almost exclusive to women and results in severe-to-profound cognitive and physical impairments. Diagnosis is made clinically, but typically individuals have a mutation in the methyl-CpG binding protein-2 (MECP2) gene (Amir et al., 1999).

Classic RTT symptoms follow an outwardly typical period of normal development. However, recent research proposes that

early development may be compromised (Einspieler, Freiling, & Marschik, 2016; Leonard & Bower, 1998; Marschik et al., 2013). Affected individuals follow a four-stage trajectory, starting between 6 and 18 months (Hagberg, 2002; Hagberg, Aicardi, Dias, & Ramos, 1983; Hagberg, Witt-Engerström, Opitz, & Reynolds, 1986; Neul et al., 2010; Witt Engerstrom, 1990). Initially, individuals experience a period of stagnant psychomotor development (stage 1) followed by a period of regression between the ages of 1 and 4 years (stage 2). Regression consists of loss of previously acquired purposeful hand skills, gait abnormalities and the emergence of hand stereotypes

[The copyright line for this article was changed on 06 March 2020 after original online publication.]

including hand wringing, clapping and tapping (Neul et al., 2010). The regression period further includes impaired communication and social withdrawal. Stage 3 consists of a period of stagnation before motor deterioration (stage 4) which can occur years later. The progressive deterioration will eventually result in individuals being unable to walk, talk and use their hands functionally (Sigafoos et al., 2009).

Individuals commonly experience associated comorbidities including epileptic seizures, impaired sleep, growth impedance and periods of incongruous laughing/screaming (Cass et al., 2003; Cianfaglione, Hastings, Felce, Clarke, & Kerr, 2015; Neul et al., 2010; Reilly & Cass, 2001; Young et al., 2007). In addition, individuals with RTT experience autonomic abnormalities in the form of breath holding, hyperventilation and abdominal bloating (Mackay et al., 2017). Three-quarters of women survive by the age of 25 years (Laurvick et al., 2006).

Research into RTT has primarily focused on addressing the phenotypic impairment and medical interventions. Despite the lifelong challenges individuals with RTT experience, to date there has been only limited research into non-medical interventions. Sigafoos et al. (2009) highlight the challenge in ranking intervention goals, given the range of impairments and the profound nature of them. Researching communication skills interventions is thought to be imperative given the nature of speech loss and restricted communicational abilities (Sigafoos et al., 2009).

A systematic review into communication interventions in RTT (Sigafoos et al., 2009) across nine studies with a total of 31 participants (aged between 2 and 17 years) concluded that the paucity of research in the area was impeding development of evidence-based practice and that the extant research was of poor quality. Sigafoos et al. (2009) proposed suggestions for improvements in experimental design, including the need for pre-intervention assessments, follow-up, generalizability, reliability and procedural data. Since their review, there have been developments in the use of music therapy, motor skills interventions, attentional training and cognitive rehabilitation.

The most prevailing interventions in RTT have been into assistive technologies. A systematic review into assistive technology (any item, piece of equipment, software program or product system that is used to increase, maintain or improve the functional capabilities of persons with disabilities in individuals) with intellectual disabilities (Perelmutter, McGregor, & Gordon, 2017) found it to be a helpful resource. However, the participants within these research studies did not present with the profound cognitive and physical impairments associated with RTT. Longitudinal research into eye gaze assistive technology in individuals with profound physical and communication impairments found improvements in the ability to communicate effectively using eye gaze if interventions are practised (Borgestig, Sandqvist, Parsons, Falkmer, & Hemmingsson, 2016).

The use of augmentative and alternative communication (AAC) strategies has been proposed as pivotal for individuals with RTT (Sigafoos et al., 2009, 2011). Research into the use of AAC strategies such as picture exchange communication systems (PECS) and vocal

output communication aids (VOCA) in individuals with an intellectual disability has been positive (Lancioni, et al., 2008, 2008a,b). Recent research into RTT has introduced the use high-tech AAC systems such as eye gaze technology to assist in the development of broader, more complex communication skills (Simacek, Reichle, & McComas, 2016).

## 1.1 | Study rationale

Sigafoos et al. (2009) indicated that despite positive outcomes for 84% of the participants, the evidence for communication interventions in RTT remains inconclusive. Furthermore, the 2009 review was limited to communication interventions. The recent developments in assistive technology and AAC intervention technology have not been systematically reviewed in the RTT population. Therefore, the current review aimed to systematically review the quality and efficacy of all non-medical interventions that have been used in Rett syndrome.

## 2 | METHOD

The current systematic review methodology was based on Higgins & Green (2011), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (Moher, Liberati, Tetzlaff, & Altman, 2009).

### 2.1 | Search strategy

The Embase (1980), PsycINFO (1806) and MEDLINE (1980) electronic databases were searched by the first author (AA). Given the limited literature on Rett syndrome interventions, no date restrictions were applied, but the search was limited to papers published in English. The following search string was used: "Rett Syndrome" AND "Interventions." The references of all initially identified were subsequently hand-searched for additional studies. In addition, the Sigafoos et al. (2009) references were searched to identify related studies. The search sought to identify papers where search terms appeared in the title, abstract or keywords.

### 2.2 | Inclusion and exclusion criteria

The review was limited to peer-reviewed articles, and the so-called "grey literature" (dissertations, conference abstracts and letters to the editor) was excluded. Studies were included if they were primarily about non-medical interventions for RTT, and papers reporting pharmacological and other medical interventions were excluded. The author chose to exclude medical interventions, firstly due to the range of potential medical interventions for RTT which might be outside the authors' area of expertise. Secondly, it was felt that non-medical interventions were largely under-represented within the literature, and therefore, a review

of the literature would allow for an increased profile of the importance of non-medical interventions.

The search terms used were intended to have a high sensitivity and low specificity so as to capture a wide range of potential interventions from a variety of disciplines which might use differing or unfamiliar terminology which may have otherwise been missed. The initial search scope was manageable ( $n = 353$ ); if this was a significantly larger number, the search terms would have been amended to balance the sensitivity and specificity more efficiently.

## 2.3 | Search results

The abstracts were downloaded to a reference manager. Titles and abstracts were screened, and relevant full texts were downloaded. The initial search yielded  $N = 353$  papers, which were reviewed by the first author (AA) using the inclusion and exclusion criteria. This resulted in  $N = 333$  papers being rejected on the grounds that they were duplicates, conference papers, phenotype studies, review studies, systematic reviews, pharmacological or medical intervention or assessment studies. The reference list yielded two further papers that were included in the review. An independent researcher replicated this process, and any discrepancies around eligibility were discussed and resolved. A total of  $N = 22$  papers were included in the final review. Figure 1 summarizes the PRISMA search process (Moher & Tetzlaff, 2009). The lack of randomized controlled trials and the heterogeneity of the studies did not allow for a meta-analysis (Centre for Reviews & Dissemination, 2009).

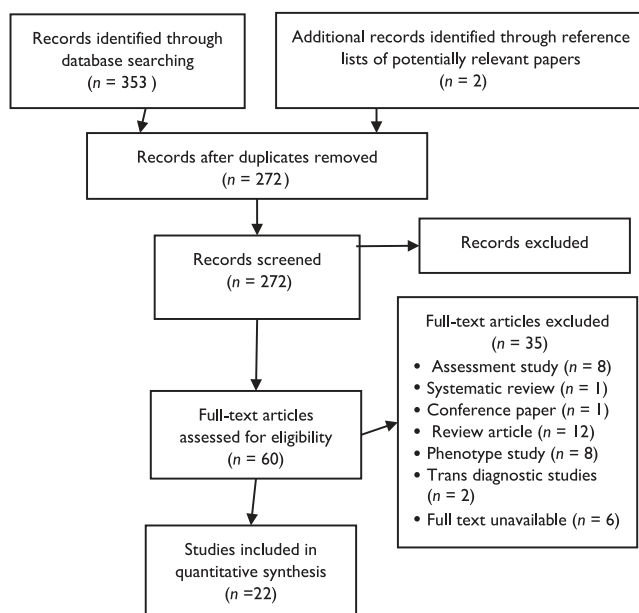


FIGURE 1 PRISMA flow diagram

## 2.4 | Data extraction

Sample data including year of publication, participant characteristics, current functioning and setting were extracted (Table 1). Study characteristics were also extracted including target behaviour and variables, research design, formal measures, intervention and results (Table 2).

## 2.5 | Quality measure

The Quality Appraisal Tool for Case Series [QATCS] (Moga, Guo, & Harstall, 2012) was used as recommended by Zeng et al (2015) and is a 20-item tool specifically developed for case series for a variety of interventions, with each item being scored as Yes, No, Unclear or Partial. Whilst it does not provide for numeric scoring, recent systematic reviews have assigned one point for Yes and half a point for Unclear or Partial responses (Auger, Hernando, & Galmiche, 2017; Roland, Skillington, & Ogden, 2017). In its original form, studies with a score above 14 are deemed to be methodologically adequate (Auger et al., 2017).

The QATCS is designed to be tailored to specific reviews (Guo, Moga, Harstall, & Schopflicher, 2016). As such, the tool was modified for the current review and five items were omitted: multicentre study (item 3), consecutive recruitment (item 4), co-intervention description (item 9), losses (item 16) and participants entering at similar points in their disease (item 7). It was thought that the nature of researching rare genetic syndromes such as RTT would mean that such items would not be achieved because of the small  $n$  numbers of recruitment. Thus, each study in the current review was scored 0–15, and following Auger et al.'s (2017) criteria, a score of 9 or above was deemed to reflect acceptable methodological quality. For quality rating items, see Table 3.

## 2.6 | Inter-rater reliability

The article selection stage required removing duplicates, grey literature and medical interventions. Data quality was initially scored by the first author (AA). After this, a second reviewer independently assessed 20% of the papers against the criteria. A kappa of 0.56 was attained, indicating a moderate level of reliability (Altman, 1991). All ratings fell within the same cut-off scores. Any disagreements were resolved via discussion.

## 3 | RESULTS

### 3.1 | Quality ratings and exclusions

Of the studies reviewed, 13/22 were scored as being of acceptable quality. Quality ratings ranged from 3.5 to 11 (mean = 9), with a possible association between the year of publication and quality rating. Furthermore, the types of interventions used appeared to change over time. For example, earlier interventions had a tendency to focus on

**TABLE 1** Sample characteristics data table

No.	Study	Cohort characteristics	Current functioning				Setting
			Communication ability	Repetitive mannerisms	Ambulatory capacity	Additional information	
1	Sharpe and Ottenbacher (1990)	N = 1, F, aged 5	No significant speech	<i>Not available</i>	Unsteady gait severely delayed fine motor skills feeding assistance	<i>Not available</i>	School
2	Sharpe (1992)	N = 2, F, aged 5	<i>Not available</i>	N1 stereotypic hand-to-mouth and rocking behaviours N2 stereotypic hand-to-hand behaviour patterns, would attempt to grasp a cracker when placed in front of her using a rhythmical raking-mass grasp pattern whilst maintaining a modified version of the stereotypic hand behaviour. Neither subject demonstrated any functional hand movements	<i>Not available</i>	Neither subject had ever used hand splints	School
3	Sullivan, Laverick, and Lewis (1995)	N = 1, F, aged 3	Some eye contact and some social smiling	<i>Not available</i>	Unable to walk or talk	<i>Not available</i>	School
4	Evans and Meyer (1999)	N = 1, F, aged 5	Limited social and communication (no expressive verbal language or formal communication skills)	Repetitive hand mannerisms	Ambulatory and unable to grasp objects	Described as "severely mentally retarded"	Special education programme
5	Koppenhaver et al. (2001)	N = 6, F, aged 3–7	All exhibited severe communication impairment as evidenced by limited to no intelligible speech. N = 1 spoke, looked at people or objects to indicate attention, wants or needs. N = 2–6 communicated through a variety of non-conventional gestures and vocalizations	<i>Not available</i>	N1–N3 Were able to ambulate independently, N4–N5 required physical assistance such as hand-holding, and N6 used a manual wheelchair that she could not self-propel. Participants were perceived as functioning in the range of severe-to-profound mental retardation	<i>Not available</i>	School
6	Yasuhara and Sugiyama (2001)	N = 3, F, aged 4–6	All exhibited no speech ability	<i>Not available</i>	All able to sit by self	<i>Not available</i>	Hospital

(Continues)

TABLE 1 (Continued)

No.	Study	Cohort characteristics	Current functioning				Setting
			Communication ability	Repetitive mannerisms	Ambulatory capacity	Additional information	
7	Hetzroni, Rubin, and Konkol (2002)	N = 3, F, aged 8–10	All exhibited non-verbal functional speech and used various communication methods. N1 interacts with adults by approaching them. N2 appeared to make choices by gazing at graphic representations of objects. N3 was able to point head to indicate choice	<i>Not available</i>	N1 walks with a wide gait N2 walks with a wide gait, but tended to walk asymmetrically. N3 walked independently with unstable gait and some assistance	All stage III No functional use of hands	School
8	Elefant and Lotan (2004)	N = 1, F, aged 9	No alternative communication system or even minimal communicational abilities. Gazes unfocused in space and smiles. Some vocalization, which increase when she is being sung to, when she is excited, and when her vocalization is being imitated	<i>Not available</i>	Walks with considerable support and sits with external support	<i>Not available</i>	Not stated
9	Lotan, Isakov, and Merrick (2004)	N = 4, F, aged 8–11	<i>Not available</i>	<i>Not available</i>	<i>Not available</i>	Rett stage III (no further information provided)	School
10	Elefant and Wigram (2005)	N = 7, F, aged 4–10	<i>Not available</i>	<i>Not available</i>	Two participants are not ambulant	Six girls were in stage III, the “plateau stage.” One girl was in stage IV, the “late motor deterioration stage”	Not stated
11	Bergström-Isacsson, Julu, and Witt-Engerström (2007)	N = 21, 20F, 1M, aged 3–44	<i>Not available</i>	<i>Not available</i>	<i>Not available</i>	<i>Not available</i>	National Rett Center
12	Fabio, Giannatiempo, Oliva, and Murdaca (2011)	N = 12, F, aged 6–26,	All unable to speak	All had pervasive hand stereotypies	Ambulation was preserved in all girls	All in post-regression phase, severely mentally retarded All showed little or no purposeful hand use	School

(Continues)

TABLE 1 (Continued)

No.	Study	Cohort characteristics	Current functioning				Setting
			Communication ability	Repetitive mannerisms	Ambulatory capacity	Additional information	
13	Meir Lotan, Schenker, Wine, and Downs (2012)	N = 3, F, aged 3–5	Not available	Not available	Not available	Not available	Not stated
14	Bartolotta & Remshifski (2013)	N = 4, F, aged 5–14	Three participants were reported to vocalize (no word production) and able to use augmentative and alternative communication (AAC) strategies (opportunities for choice making, use of single switches and picture boards). All girls were reported to use eye gazing for communication purposes	Not available	Not available	Clinical stage III (pseudostationary period)	School
15	Fabio, Castelli, Marchetti, and Antonietti (2013)	N = 1, F, aged 21	No meaningful words or eye contact	Hand stereotypes	Can walk/run for hours turning in a room	Clinical stage IV of RS Inability to hold, pick up or grasp objects	School and home
16	Stasolla and Caffo (2013)	N = 2, F, aged 12–17	Participants with lack of speech and withdrawal, some vocalizations	Stereotyped behaviours (i.e. body rocking for N1 and hand washing for N2)	Motor impairments with dystonic movements, although they were able to make some step responses in their walker device	All participants experienced hyperventilation, scoliosis, seizures and epilepsy. Severe-to-profound intellectual and developmental disabilities. limited use of hands, profound deficits in adaptive behaviours	Home
17	Hackett, Morison, and Pullen (2013)	N = 1, F, aged 4	No eye contact	Not available	Not available	No purposeful hand movements	Not stated
18	Stasolla et al. (2014)	N = 3, F, aged 8–10	Communication impairments (i.e. lack of speech, but some vocalizations), Unable to perform request and choice of needed items to communication partners	Stereotyped behaviours (i.e. body rocking for n1, hand tipping for n2 and hand washing for n3)	None of the girls had awareness of the sphincteric control and all motor impairments, with failure in ambulation responses	Seizures and hyperventilation. Severe-to-profound developmental disabilities	Home

(Continues)

TABLE 1 (Continued)

No.	Study	Cohort characteristics	Current functioning				Setting
			Communication ability	Repetitive mannerisms	Ambulatory capacity	Additional information	
19	Lancioni et al. (2014)	N = 1, F, aged 21	No speech or communication. No interaction with objects		Non-ambulatory. Sat in wheelchair		Home
20	Stasolla et al. (2015)	N = 3, F, aged 9–12	Lack of speech, autonomous locomotion	Repetitive hand stereotypic behaviours but able to pick up familiar objects	<i>Not available</i>	Severe-to-profound developmental and intellectual disabilities	Home
21	Simacek et al. (2016)	N = 2, F, aged 7–27	Unable to use gestures or vocalizations, able to display idiosyncratic responses that allowed researchers to assess preference for items and/or activities	<i>Not available</i>	<i>Not available</i>		Home
22	Simacek, Dimian, and McComas (2017)	N = 1, 3-year-old girl <sup>a</sup>	<i>Not available</i>	Frequent repetitive behaviours of clapping hands, mouthing hands and mouthing other objects	Ambulatory, with gross motor abilities to walk, step up and down to navigate stairs with supervision, and to bend down and pick up or briefly hold small items. Hand function ability included self-feed and pick up lightweight items and to press buttons to activate musical toys		Home

Note: <sup>a</sup>Two further participants with autism spectrum disorder

physical mobility restriction such as repetitive hand movements via the use of hand splints and restraint (1, 2, & 4), whereas more recent interventions have focused on increasing the brevity of individuals' communication ability. Lower quality papers failed to report a clear hypothesis, objective or aim (1, 4, 6 & 8). They further lacked a clear intervention description (3, 4, 6 & 13), a priori outcome measures (1, 3 & 8) and follow-up data (2, 3, 6 & 8). Both the high- and low-quality papers would have benefitted from improved clarity of their eligibility criteria, statements of blindness of researchers, estimates of random variability, adverse events disclosure and competing sources of interest statements. See Table 4 for quality rating scores. The papers that reached acceptable levels of quality will be reported upon (N = 13).

## 3.2 | Characteristics of studies

### 3.2.1 | Participants

The number of participants in each study ranged from 1 to 21 (mean = 4.6) and represented N = 60 participants in total. Ten of the studies reported on from 1 to 4 participants (7, 9 & 15–22) who were recruited via either existing cohorts or non-specified recruitment methods. The study with the largest participant number (N = 21; Study 11) was recruited via the Swedish National Rett Center. The second largest participant number study (N = 12; Study 12) was recruited via the Italian Rett Association.

TABLE 2 Study characteristics data table

No.	Article	Target behaviour and variables	Design	Measures	Intervention	Number of sessions/dose	Results	Quality score (0–15)
1	Sharpe and Ottenbacher (1990)	Physical/movement IV—elbow restraint DV—feeding ability	Single-study ABAB	Finger-feeding skills	Elbow restraint	32 days (16 days intervention and 16 days control) Intervention sessions between 2 min 39 s and 5 min 10 s of duration	Modest improvements in amount of cereal consumed and in time required to complete task No effect size or statistical tests completed	8.5
2	Sharpe (1992)	Physical/movement IV—hand splints and elbow orthosis DV—stereotypic movements and toy use	Multiple-baseline	Observation of stereotypic behaviour and hand wringing	Hand splint	30 sessions (5 days per week), random assignment to treatment phases for condition (bilateral hand splints, elbow orthotics or no intervention). Sessions over 5 min of duration of free time and 5 min of duration of toy-play condition	1) No decreased stereotypic movements 2) No increased feeding skills 3) No increase in handwriting following withdrawal No effect size of statistical tests completed	7.5
3	Sullivan et al. (1995)	Communication IV—contingency intervention programme DV—positive emotional response	None stated	Head and hand activation frequency	Contingency intervention programme (Sullivan, 1993)	40 sessions of 14 min of duration over 1 year	Modest and inconsistent increase in hand use No effect size of statistical tests completed	5.5
4	Evans and Meyer (1999)	Behaviours IV—individualized Intervention programme Condition 1—teaching a voluntary manual response (using communicational instructions and physical movement of hands) Condition 2—revised intervention that used playful, complementary interactions DV—hand stereotypes (1) and development of informal gestures (2)	ABAB	1) Frequency of behaviours; body rocking, hand mannerisms, rubbing face, mouthing body, cry, shriek, blowing and vocalizing 2) Frequency of gestures	Individual educational plan (IEP) including non-contingent restraint of hand mannerisms (condition 1) and use of standard prompting and social reinforcement	Condition 1—3x per day, 10 min of duration for six months (unclear if the intervention was consistent over six months). Data collected over 18 observation sessions over six months Condition 2—3x per day for 10 min of duration over six months	1) No reduction in behaviours and restraint increased use of other behaviours (blowing) 2) No evidence of hand gesture acquisition Conclusions: Teaching alternative behaviours is less effective than focusing on communicative behaviours that are present already	8.5

(Continues)



TABLE 2 (Continued)

No.	Article	Target behaviour and variables	Design	Measures	Intervention	Number of sessions/dose	Results	Quality score (0–15)
5	Koppenhaver et al. (2001)	Communication IV—storybook intervention DV—communication ability	Multiple-baseline	Coding of storybook Interactions coded by communication mode and communication act (e.g. use of picture symbols and speech-generating devices to label pictures)	Introduction of a variety of assistive technologies on the storybook reading and communication interactions. Parental training of storybook interactions (including attribute meaning to communicative attempts, ask questions to encourage communication and use of time delay and prompts to encourage accurate use of speech-generating device)	Families attended 5 monthly information sessions across four months. No further information	Substantial increases in frequency of symbolic communication and labelling commenting were reported in all six participants without highly structured or long-term interventions. Symbolic communication, increased with frequency of (1) introduction of communication technologies; and (2) increasing mothers' awareness of communication modes of their daughters No effect size of statistical tests completed However, there were no sessional data available and the intervention was not strictly controlled for	9 <sup>a</sup>
6	Yasuhara and Sugiyama (2001)	Communication IV—music therapy DV—hand grasping	No evidence of experimental design	Coding of recorded sessions	Individualized music therapy including instrument play, engagement in song and choices	40 sessions over 30 min of duration	The authors report that the music therapy showed a degree of mental and physical development. However, there was no evidence of operationally defined behaviours or treatment No effect size of statistical tests completed	5
7	Hetzroni et al. (2002)	Communication IV—assistive technology DV—learning	Multiple-probe design	Symbol set identification	Use of individualized computer-based and alternative communication (ACC) system (choice of picture, symbol or word by using eye gaze and moving nose or head)	Session lengths were variable depending on how long the intervention took. Unclear information regarding intervention dosage	The authors report a steady learning curve across symbol sets and a partial retention of knowledge throughout maintenance probes. The results suggest that girls with Rett syndrome are capable of matching spoken words to symbols when provided with meaningful instruction. However, some baseline results also improved; therefore, improvements should be interpreted cautiously No effect size of statistical tests completed	10 <sup>a</sup>

(Continues)

TABLE 2 (Continued)

No.	Article	Target behaviour and variables	Design	Measures	Intervention	Number of sessions/dose	Results	Quality score (0–15)
8	Elefant and Lotan (2004)	<i>Communication</i> IV—music and physical therapy DV—attention span and communication (non-verbal expression, vocalization and verbal ability)	None stated	None clearly defined	13-phase combined music and physical therapy	2 x ¼ hour sessions per week. No information regarding duration of treatment	The authors state the intervention approach has proved effective in improving communication skills No effect size of statistical tests completed However, the study was reported in narrative form and did not include an experimental design, outcome measures or data	3.5
9	Lotan et al. (2004)	<i>Physical/motor</i> IV—physical exercise programme DV—physical fitness and general functioning	Paired t test pre/post design	Pulse measurements and functional skills scale	Treadmill training	Daily training over a two-month period (each participant receiving between 36–50 sessions). Graduated sessions from 5 to 30 min of duration (average 19.9 min of duration) Pre- and post-motor improvements, high correlational linkage ( $p < .0001$ ) between functional improvement and physical fitness	Improved physical fitness and general functional abilities	10.5 <sup>a</sup>
10	Elefant and Wigram (2005)	<i>Communication</i> IV—music therapy DV—learning and communication ability	A single-subject, multiple-probe design	Observed frequency of selection of communication (eye gaze, nose pointing, touching picture/words)	Music therapy including song selection (from symbols) and confirmation of selection	3 sessions per week between 20 and 30 min of duration. 5 months of duration (including baseline, intervention and maintenance). Total 22 sessions	The authors report evidence of learning in all participants and responses to music therapy. No effect size of statistical tests completed However, this research did not present baseline data and provide the data to support their conclusions (apart for one participant)	7.5

(Continues)

TABLE 2 (Continued)

No.	Article	Target behaviour and variables	Design	Measures	Intervention	Number of sessions/dose	Results	Quality score (0–15)
11	Bergström-Isacson et al. (2007)	Communication IV—music and vibroacoustic therapy (VT) DV—brainstem activity	Controlled within-subject study	Brainstem activity (parasympathetic and sympathetic responses)	Music therapy and VT	1 session of 10 min of VT and 10 min of music therapy	Overall, "calming music" evoked parasympathetic responses and "activating music" evoked sympathetic responses in the responders. Horn music and vibroacoustic were effective stimuli that evoked responses in all the subjects in this group. Calming music together with the vibroacoustic stimulus for dual stimulation became less effective and failed to evoke autonomic responses in some subjects No effect size of statistical tests completed	10 <sup>a</sup>
12	Fabio et al. (2011)	Communication IV—attention training DV—requests and attention	Pre-test/post-test study design	Attention span coding, frequency of help given, Vineland score and the number of correct answers	Attentional training	Study over 9 months (including evaluation, daily training, repeat assessment, daily training and repeat assessment). No information on frequency or length or sessions	Reported it is possible to modify attention span [ $F(2,35)=7.33; p = .16$ ] and decrease the dependence on help in cognitive training. Controlling posture and physical containment decreases stereotypies (necessity to remove all external stimuli that make it difficult to work on the target stimulus, thus enhancing their selective attention). Increase on most of the Vineland areas [ $F(2, 22)=39.72; p=.001$ ] (communication, daily ability, socialization and motor skill)	10 <sup>a</sup>

(Continues)

TABLE 2 (Continued)

No.	Article	Target behaviour and variables	Design	Measures	Intervention	Number of sessions/dose	Results	Quality score (0–15)
13	Meir Lotan et al. (2012)	Physical/ Motor IV—motor skills intervention DV—physical improvements	AB design	The Rett Functional Evaluation Scale and Rett Syndrome Gross Motor Scale. Functional performance in the domains of self-care and social function was assessed using the Pediatric Evaluation of Disability Inventory (PEDI), and hand function was measured with a scale developed based on the Hand Apraxia Scale	Conductive education (CE). An educational approach aimed to improve psychosocial development, coordination, motor control and activity participation. The specific nature of the intervention was not described	No dosage or sessional data available	The authors report improvements in gross motor function. No effect size of statistical tests completed Hand function and social skills were similar at baseline and 16/17 months following intervention. Self-care skills were the same or declined (n1) following the intervention period	8.5
14	Bartolotta and Remshifski (2013)	Communication IV—coaching communication partners to recognize and respond to communication acts DV—communication behaviours	Quasi-experimental repeated-measures design	Frequency of communication behaviours (vocalizations, head and body movements, gestures, facial expressions or use of AAC strategies)	Coaching sessions over four phases (baseline, coaching intervention, post-coaching session and follow-up maintenance) using recorded data and data analysis of behaviours and AAC strategies	No dosage or sessional data available	No effect size or statistical tests completed Increase in the communication partners' awareness (following coaching) of the girl's communication attempts corresponds with a change in the communication partners' behaviour and a change in the communicative behaviour of the child with RTT	8

(Continues)

TABLE 2 (Continued)

No.	Article	Target behaviour and variables	Design	Measures	Intervention	Number of sessions/dose	Results	Quality score (0–15)
15	Fabio et al. (2013)	Communication IV—cognitive rehabilitation training DV—reading–writing ability	Single-case research. Short-time-series design	Number of attempts to reach criteria for words, letters and syllables	Cognitive rehabilitation training based on Feuerstein's modifiability and mediated learning theory (Feuerstein, Rand, and Rynders, 1988). Intervention was run over two-phase pre-training and training	Pre-training ability sessions: 4 sessions (50 min of duration) per week for 3 years Discrimination of words training: 4 sessions (50 min of duration) per week for 2 ½ years Separation of words training: 4 sessions (50 min of duration) per week 1 year Separating syllables: 4 sessions (50 min of duration) per week for 6 months Sentence construction: no session information	Learning of 16 specific words [Z(16) = 4.02, $p < .05$ ] (names and familiar objects) reading syllables [Z(18) = 3.72, $p < .05$ ] and letters [Z(19) = 1.94, $p < .05$ ]	10 <sup>a</sup>
16	Stasolla and Caffo (2013)	Communication IV—assisted technology DV—performance, happiness and reduction in stereotypes	Multiple-probe design	Frequency of microswitch activation, indices of happiness and indices of stereotyped behaviours	Assisted technology (microswitch) for five minutes, 3–4 times per day over six months	3–4 sessions per day (5 min of duration), 4 days per week for six months	Increase in performance of microswitch use and of indices of happiness and a decrease in stereotyped behaviours for both participants during intervention phases. Indices for happiness difference for one participant were reported on and statistically significant ( $p < .01$ )	11 <sup>a</sup>
17	Hackett et al. (2013)	Communication IV—music therapy DV—hand use and turn taking	Single-case retrospective video analysis	Frequency of hand use and turn taking	Music therapy over 14 sessions	14 treatment sessions (30 min of duration)	Increased frequency of hand use and turn taking No effect size or statistical tests completed	9 <sup>a</sup>
18	Stasolla et al. (2014)	Communication IV—PECS and VOCA DV—communication	Alternating-treatment single-case design	Number of items requested and chosen independently, stereotyped behaviours and indices of happiness	PECS sessions and VOCA sessions	2–4 sessions per day (10 min of duration), 5 days per week approximately over approximately 4 months	PECS and VOCA improve communication abilities via the introduction of making request and choice of items. All differences between baseline and intervention phases for all participants involved were statistically significant ( $p < .01$ ). Both intervention strategies are successful by increasing participants' positive mood (i.e. indices of happiness) and by reducing stereotyped behaviours	11 <sup>a</sup>

(Continues)

TABLE 2 (Continued)

No.	Article	Target behaviour and variables	Design	Measures	Intervention	Number of sessions/dose	Results	Quality score (0–15)
19	Lancioni et al. (2014)	Communication IV—assisted technology {microswitch} DV—microswitch responses and level of happiness	ABAB	Level of response and stimulation input and objective measures of happiness	Microswitch-assisted technology	1 (5 min of duration) session per day, five days per week across 11 total sessions	Increase in microswitch responses and level of happiness for both participants during the intervention phases of the study No effect size or statistical tests completed	10 <sup>a</sup>
20	Stasolla et al. (2015)	Communication IV—assistive technology DV—responses and stereotypes behaviour	Multiple-probe design	1. Number of objects inserted in a container 2. Happiness indices 3. Intervals of stereotypic behaviours	Assisted technology (sensors and personal computer)	2–4 sessions (10 min of duration) per day, 4 days a week across a total 225 sessions (over a six-month period)	Reduction in stereotypic behaviours, increase in adaptive responses and increase in indices of mood All differences between baseline and intervention phases were statistically significant, for all participants involved ( $p < .01$ )	9 <sup>a</sup>
21	Simacek et al. (2016)	Communication IV—AAC intervention (speech-generating device with eye gaze or touch screen technology) sessions DV—responses	Case series. Within participant using concurrent multiple-baseline design	Independent accurate selection (via pressing or eye gaze) of target request	Use of speech-generating device (SGD) to increase aided AAC using either pressing (n1) or eye gaze (n2) to select preferred item or choice	Between 3 and 6 sessions per day (between 5 and 15 min of duration) with 1–2 sessions per week across six months (N1) or 8 months (N2)	Acquisition of requesting skills for $n = 1$ which were sustained. Increasing of skills in $n = 2$ ; however, the skills were not sustained when prompt was faded No effect size or statistical tests completed	11 <sup>a</sup>
22	Simacek et al. (2017)	Communication IV—parent-implemented communication intervention with remote coaching via telehealth DV—augmentative and alternative communication (AAC) responses	Adapted multiple-probe design with an embedded ABAB design	AAC responses (hitting a microswitch) and individual idiosyncratic responses (hitting the tray of high chair, extending one or both hands towards parent or item and walking towards parent)	Parent-implemented functional communication training (FCT) with telehealth as a service delivery mechanism	Functional Analysis sessions; 5 sessions of each condition. 5 min of duration with no more than 10 sessions per day. No information of how many days Parent-implemented functional communication training: 7 sessions per day (5 min of duration). No information of how many days	AAC response was learnt across three contexts. No effect size or statistical tests completed However, the participant with RTT did not retain the learning of responses. The authors propose that different reinforcement schedules might further assist learning following intervention. In addition, the need for future research of intervention fading strategies	9 <sup>a</sup>

<sup>a</sup>Rated acceptable quality and included in the review.

All study participants had a diagnosis of RTT, and all but one participant were female (11). One study (22) included two further participants with autism spectrum disorder (the results of which were excluded from this review). The authors specified specific ages for participants in 10 of the thirteen studies. The remaining three studies only specified age ranges across participants (Studies 9, 11

and 12). The participant ages ranged from 3 to 44 years. There was variability in the reporting of functioning and stage of RTT, with the latter only reported in four studies, namely 7, 9 and 12 (stage III) and 15 (stage IV). Participants were reported to be severe-to-profound intellectually disabled (5, 12, 16, 18 & 20) and/or with no functional speech (5, 7, 12, 15, 16 & 18–21).

**TABLE 3** Quality rating criteria

Study objective	
1.	Was the hypothesis/aim/objective of the study clearly stated?
Study design	
2.	Was the study conducted prospectively?
Study population	
5.	Were the characteristics of the patients included in the study described?
6.	Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?
Intervention and co-intervention	
8.	Was the intervention of interest clearly described?
Outcome measures	
10.	Were relevant outcome measures established a priori?
11.	Were outcome assessors blinded to the intervention that patients received?
12.	Were the relevant outcomes measured using appropriate objective/subjective methods?
13.	Were the relevant outcome measures made before and after the intervention?
Statistical analysis	
14.	Were the statistical tests used to assess the relevant outcomes appropriate?
Results and conclusions	
15.	Was follow-up long enough for important events and outcomes to occur?
17.	Did the study provide estimates of random variability in the data analysis of relevant outcomes?
18.	Were the adverse events reported?
19.	Were the conclusions of the study supported by the results?
Competing interests and sources of support	
20.	Were both competing interests and sources of support for the study reported?

### 3.2.2 | Target behaviours

Out of the 13 papers, eleven broadly related to communication interventions (5, 7, 12 & 15–22). The remaining papers targeted physical fitness (Study 9) and brainstem activity (11). Of the communication interventions, eight studies specifically targeted either learning of a new communication skill via symbols, words, labels and microswitches or using communication aids to make choices and requests (5, 7, 12, 16 & 18–22). Other target behaviours were frequency of hand use and turn taking (17) and increase in attention span (12).

Seven studies measured secondary dependent variables alongside the main target variables (5, 9, 12, 16, 18–20). These included increase of parental awareness of child's communication modes (7), functional motor improvements (9), adaptive behaviours (12), dependence on help from others (12), happiness (16 & 19), mood (18, 20) and adaptive responses (20). Target behaviour of the RTT phenotype "hand stereotypes" was measured as a secondary variable in four studies (12, 16, 18 & 20).

### 3.2.3 | Intervention procedures

In the studies that reported on communication procedures, eight included the use of assistive technology or AAC interventions (5, 7, 16 & 18–22). Interventions included the use of assistive technologies such as storybook (5), microswitch (16 & 19), PECS and VOCA (18) and

sensors and a personal computer (20). Interventions using AAC included computer-based ACC system requiring learning of choices of a picture symbol or eye gaze and head/nose movements (7), use of a speech-generating device using eye gaze or touch (21) and microswitch responses (22). Further communication interventions used music therapy (11 & 17), attentional training (12) and cognitive rehabilitation training (15). The physical exercise study (9) included a treadmill programme.

### 3.2.4 | Study design

Of the 13 studies, six used a multiple-baseline design (5 & 21) or multiple-probe design (7, 16, 20 & 22). Two studies used pre-test/post-test design (9 & 12). Other experimental designs included controlled within-subject study design (11), ABAB design (19) and alternative single-case research designs (15 & 17–18).

### 3.2.5 | Types of outcome measure

The majority of the studies used individualized frequency measures to measure target behaviours via the use of analysing video or in-session recordings (5, 7, 12 & 15–22). Three studies used objective measures of indices of happiness (16, 18 & 20). Two studies measured autonomic nervous system signals including pulse (9) and EEG activity

**TABLE 4** Quality ratings

1	Sharpe and Ottenbacher (1990)	P	Y	Y	N	Y	N	U	Y	Y	Y	U	N	N	Y	N	8.5
2	Sharpe (1992)	Y	Y	Y	N	Y	Y	N	Y	U	N	N	N	N	Y	N	7.5
3	Sullivan et al. (1995)	Y	Y	Y	N	P	N	N	N	U	N	Y	N	N	U	N	5.5
4	Evans and Meyer (1999)	P	Y	Y	N	N	Y	N	Y	Y	Y	Y	N	N	Y	N	8.5
5	Koppenhaver et al. (2001)	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	N	Y	N	9 <sup>a</sup>
6	Yasuhara and Sugiyama (2001)	N	Y	Y	N	N	Y	N	N	N	N	Y	N	N	Y	N	5
7	Hetzroni et al. (2002)	Y	Y	Y1	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	N	10 <sup>a</sup>
8	Elefant and Lotan (2004)	N	Y	Y	N	Y	N	N	N	N	N	U	N	N	N	N	3.5
9	Lotan et al. (2004)	Y	Y	Y	P	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	10.5 <sup>a</sup>
10	Elefant and Wigram (2005)	Y	U	Y	N	Y	Y	N	Y	Y	N	Y	N	N	N	N	7.5
11	Bergström-Isacson et al. (2007)	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	10 <sup>a</sup>
12	Fabio et al. (2011)	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	10 <sup>a</sup>
13	Lotan et al. (2012)	Y	Y	N	N	P	Y	N	Y	Y	N	Y	N	N	Y	Y	8.5
14	Bartolotta and Remshifski (2013)	Y	Y	Y	N	Y	Y	N	Y	Y	N	N	N	N	N	Y	8
15	Fabio et al. (2013)	Y	Y	Y	N	Y	Y	N	P	Y	Y	U	N	N	Y	Y	10 <sup>a</sup>
16	Stasolla and Caffo (2013)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	11 <sup>a</sup>
17	Hackett et al. (2013)	Y	N	Y	N	Y	Y	N	Y	N	Y	Y	Y	N	Y	N	9 <sup>a</sup>
18	Stasolla et al. (2014)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	11 <sup>a</sup>
19	Lancioni et al. (2014)	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	10 <sup>a</sup>
20	Stasolla et al. (2015)	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	N	N	Y	N	9 <sup>a</sup>
21	Simacek et al. (2016)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	N	11 <sup>a</sup>
22	Simacek et al. (2017)	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N	Y	Y	9 <sup>a</sup>

<sup>a</sup>Above quality threshold.

(11). One study additionally used a standardized measure of adaptive behaviour (12). Whilst the majority of the studies included inter-rater reliability scoring across the measures, the results may be vulnerable to biases from the coders, who were affiliated with the study given the studies did not report the design being blinded (apart from Study 17).

### 3.2.6 | Outcomes

Table 2 shows the specific outcomes for each study. Results were found to be solely positive on the target behaviours in eleven of the 13 studies (5, 7, 9, 11–12 & 15–20). In Study 21, the results were mixed for the participants. The results of Study 22 noted that the target behaviour was achieved (learning); however, retention of the target behaviour was not achieved. None of the studies reported adverse effects or reported a decrease in target skills or ability.

### 3.2.7 | Common methodological issues

It was not possible to assess the representativeness of the sampling frames as most studies did not report on the recruitment

sampling in adequate detail (5, 7, 9, 16, 17, 19 & 20). Similarly, it was not possible to comment on the potential for selection or response bias. The potential for biases was rarely reported, and it was noted that the earlier studies were often reported in narrative form and hence more susceptible to bias. In addition, most studies did not report information regarding other interventions that could have been delivered in parallel, which creates difficulties with respect to identifying potential confounding variables and assessing the validity of the results. In the studies that were conducted over a substantial length of time to facilitate learning, potential confounding factors such as maturation and relational variables were not reported.

## 4 | DISCUSSION

This is the first systematic review of non-medical interventions for RTT, following on from an earlier review of communication-based interventions in RTT (Sigafoos et al., 2009). Earlier studies tended to be of low methodological quality and focused on physical interventions and communication that may reflect recent changes in the types of interventions used in RTT (e.g. the move from using restraints).



Of the 13 studies included in the review, most focused on communication as the primary target intervention. In 11 of the studies, individuals with RTT showed improvement in the target behaviour and secondary targets (such as happiness or stereotypes), suggesting that such individually tailored interventions may be of benefit to individuals with RTT. The interventions found cognitive abilities such as attention and reading-writing can be increased and sustained using well-structured individualized intervention programmes such as attentional training and cognitive rehabilitation training (12, 15 & 16). In addition, global abilities or quality of life may also improve (12, 15, 16, 18–19). The use of technology such as microswitch (16 & 19), PECS and VOCA (18) and other forms of assistive technology (7, 20–22) may facilitate improved communicational abilities. The implementation of communication interventions was found to reduce stereotyped behaviours (16, 18 & 20).

The review found that there is a strong evidence base for communication interventions; however, such interventions are resource-intensive and usually of relatively high cost. Historically, computer-based assistive technology has had both high initial costs and the ongoing costs of updating the software, but the recent development of mobile devices and associated app technology may significantly reduce these costs. Individuals with less existing communicative ability (e.g. no vocalizations, or communicative hand movements) would benefit the most from “higher technology” assistive technology interventions that assist in the use of communication modes such as eye gaze technology.

Non-communication interventions were harder to draw direct conclusions from due to the heterogeneous nature of the studies and interventions. Early indications indicated that addition interventions may improve both target behaviours and secondary behaviours. Firstly, physical fitness may be improved using a low-intensity treadmill programme (9). In addition, in support of anecdotal evidence of music therapy, different musical stimuli could evoke different sympathetic and parasympathetic responses in individuals with RTT (11). In addition, the current review found that there is some evidence that the use of a music therapy intervention may assist the development of intentional communication (17). The review further indicated parental training in communication skills and interpretation may assist parental ability to understand and interpret their child's unconventional non-verbal communication signals (5). These intervention measures (treadmill, music therapy, parental skills training) require further research to be able to draw clear conclusions from both the target and secondary measures.

Overall, the interventions have been developed on an atheoretical, pragmatic participant needs-led basis. As such, the interventions themselves are generally theoretically agnostic. Future research may improve the understanding of the specific mechanisms and processes of interventions.

#### 4.1 | Limitations

Given the wide-ranging and profound nature of both physical and communication abilities individuals with RTT encounter and the age and stage of RTT, the high-quality and effective interventions were largely tailored specifically to the individuals. Therefore, the studies

were disparate from each other in terms of using similar measures, experimental conditions and interventions. It is challenging to draw firm conclusions regarding the interventions collectively. In addition, the researchers/coders were not blind to the study (besides one study), which further impedes the supposition that the changes occurred solely due to the intervention itself.

Furthermore, the rarity of RTT leads to challenges in recruitment and most reported studies are  $N = 1$  or small- $N$  designs. This compromises the possibility of undertaking more sophisticated controlled studies or trials. Given most of the studies have severe limitations in their external validity and generalizability to wider RTT populations results should be interpreted cautiously. Future research will be needed to establish the efficacy of the interventions within RTT.

A further limitation was that many of the studies in the current review did not report on the progressive nature of RTT. Depending on the RTT stage, a decline in functioning or some degree of recovery may be expected. In those studies that did specify RTT stage and age, there was no consideration of the implications of this with regard to the target outcome and the potential for it to be a confounding variable. Similarly, there was only limited reporting of comorbid medical issues and/or concurrent pharmacological interventions. The potential interaction between biological/medical interventions and environmental interventions is an area that may require further exploration.

#### 4.2 | Recommendations for clinical practice

The main aspect of the individual studies is to tailor specific clinical interventions according to the individual. An assessment of the skills individuals with RTT currently hold will inform the starting point of the intervention, and then, interventions can be built on depending on the outcome. For example, some individuals will be able to use microswitches using their motor abilities, whilst other individuals will be limited to eye gaze technologies. Similarly, assessment and outcome measures are best tailored to the individual. Additional measures, measuring secondary outcomes, will assist in the review of the efficacy of the interventions.

In terms of the choice of interventions, the recent advances in technology offer promising contributions to assisting unconventional communication strategies in the absence of traditional communication strategies. However, these resources will be inevitably more resource-intensive and expensive. Improving access to assistive technology (both low and high technology), environmental stimuli and engagement should assist in improving communication, mood and quality-of-life outcomes for individuals with RTT. “Low-tech” solutions such as PECS and VOCA should be considered when motor abilities permit, to allow for increased access with minimum financial constraints, whereas “high-tech” approaches such as speech-generating devices, microswitch and eye gaze technology may be more appropriate if the person's intellectual and motor abilities are profound (Matson, 2012).

Interventions could be developed with parental support. This will assist in upskilling the parents in recognizing communication attempts in their child. Once trained, parents could complete this alongside the existing care of their child.

Research into physical fitness in RTT highlighted the low baseline of fitness for individuals with developmental disabilities. In the light of the research, physical fitness should be considered to be incorporated into care planning of individuals with RTT to improve their baseline mobility and fitness. In typical clinical settings, individuals will already be being offered a range of support from a variety of differing disciplines. It is imperative that practice-based evidence is encouraged and shared and attempts are made to researching practice-based evidence to inform the evidence base.

### 4.3 | Recommendations for future research

The review has highlighted the need for larger participant number research. Interinstitutional, interdisciplinary and international research collaboration is required in order to increase recruitment numbers and disseminate information and clinical expertise. Future studies would benefit from increased research rigour including longitudinal data collection, multiple baselines, control studies and adequate follow-up periods. Moreover, research should include information regarding the RTT stage, participant characteristics (such as age), demographics and report on how these might influence the research findings. Further, research regarding dose frequency of interventions should be conducted. Later, research developments should focus on expanding the communication skills of individuals with RTT to broaden their communication repertoires.

Future research into physiotherapy-directed interventions is warranted to contribute to the knowledge base of physical fitness and mobility within RTT. In addition, further research is needed to investigate the efficacy of music therapy across larger sample sizes.

The early focus on parental involvement in interventions has diminished over the years, with increased focus on utilizing recent advanced software. Given most children reside in the family home, a broader research focus is required to incorporate the impact of family and interaction interventions as opposed to solely software-led assistive technology. Future research should investigate interventions that have been researched within the remit of intellectual disabilities to investigate its utility in the RTT population. For example, there is a growing evidence base of the use of intensive interaction in individuals with severe and profound intellectual disabilities. Research has reported on improved pre-verbal communication skills, maintenance of social engagement and relationships after an intensive interaction intervention (Anderson, 2006; Argyropoulou & Papoudi, 2012; Firth, Elford, Leeming, & Crabbe, 2008; Kellett, 2000, 2005; Samuel, Nind, Volans, & Scriven, 2008; Watson & Knight, 1991; Zeedyk, Caldwell, & Davies, 2009; Zeedyk, Davies, Parry, & Caldwell, 2009).

## 5 | CONCLUSION

This review of a comparatively small number of studies that meet quality rating criteria indicates that there is some evidence of

effectiveness of interventions in RTT. The results need to be interpreted cautiously given the challenges of the research rigour. However, the research presents promising insights into intervention programmes for individuals with RTT and future directions for clinical research.

### ACKNOWLEDGMENT

The authors would like to thank Olivia Ambler for assistance in inter-rater reliability coding.

### CONFLICT OF INTEREST

Dr Hare is on the editorial board for JARID.

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**How to cite this article:** Amoako AN, Hare DJ. Non-medical interventions for individuals with Rett syndrome: A systematic review. *J Appl Res Intellect Disabil*. 2020;33:808–827. <https://doi.org/10.1111/jar.12694>