

SYSTEMATIC REVIEW

Speech, language, social communication, and communication assessments in Rett syndrome: A systematic review

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Abstract

Aim: To provide a systematic overview of speech, language, and social abilities of people with Rett syndrome (RTT), and identify the most frequently used communication assessments in the literature.

Method: A systematic search of PubMed, CINAHL, ScienceDirect, ERIC, and speechBITE databases was conducted using terms synonymous with RTT, speech, language, social, and clinical assessment. Two independent reviewers screened abstracts; one reviewer conducted full-text screening, communication-related data extraction, and quality appraisal, with verification by a senior author of a subset of full-text articles.

Results: A total of 3091 papers were identified after removal of duplicates, of which 59 met inclusion criteria. Severe communication impairment emerged as a core feature of RTT, across classic and atypical variants, to differing degrees. Expressive language and speech production were most severely affected. Atypicality in all communication domains was reported both pre- and post-regression. Genetic (e.g. *MECP2* variant) and developmental (e.g. age) factors modulated ability; poorer outcomes often linked to early truncations and large deletions. Most assessments relied on caregiver report. **Interpretation:** Speech–language difficulties are ubiquitous in RTT, ranging from mild to profound. Objective assessment is limited by severe motor-speech impairment and a reliance on caregiver report; flexible and/or more granular tools are necessary. The use of both objective (e.g. acoustic analysis) and subjective (e.g. caregiver recall) measures is warranted for characterizing speech–language ability.

Rett syndrome (RTT) is a rare genetic disorder associated with severe neurodevelopmental regression, caused by variants in the X-linked methyl-CpG-binding protein 2 (*MECP2*) gene.¹ Occurring predominantly in females, RTT is a leading cause of intellectual disability, with an estimated global prevalence of 1 in 14 000 females, and a cumulative incidence of 1 in 10 000 by 12 years of age.^{2–4} RTT is characterized by the loss of acquired skills, including spoken language and purposeful hand movement, and development of other

physiological symptoms including repetitive hand stereotypies.⁵ These features emerge after near-typical postnatal development.^{6,7}

The course of RTT is described across four clinical stages (I–IV), each with a unique developmental trajectory.^{7–9} Chronologically, these are (I) early onset stagnation; (II) developmental regression; (III) pseudostationary phase; and (IV) late motor deterioration.⁹ Developmental delay is common between 6 months and 18 months of age, followed by the

Abbreviations: AAC, augmentative and alternative communication; CSBS, Communication and Symbolic Behavior Scales; *MECP2*, methyl-CpG-binding protein 2 gene; PSV-RTT, preserved speech variant of Rett syndrome; RTT, Rett syndrome; VABS, Vineland Adaptive Behavior Scales.

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regression of acquired skills until about 4 years, after which stabilization occurs.^{7,9,10} Other symptoms continue to emerge, including seizures and respiratory disturbances.^{11,12} Later stages of the disorder often involve motoric and neurological impairment, including Parkinsonian-like symptoms, although most individuals live well into middle age and beyond.^{10,13}

RTT is clinically differentiated into classic and atypical subtypes.⁵ Patients with classic RTT meet all four main clinical diagnostic criteria, while those with the atypical subtype meet at least 5 of 11 supportive criteria.⁵ Children with the preserved speech variant (PSV-RTT; also known as Zappella variant) exhibit greater speech–language recovery post-regression, including the partial restoration of verbal speech.¹⁴ In approximately 95% of cases, RTT results from *de novo* loss-of-function variants in *MECP2*.^{5,15} This may restrict neural function, given that *MECP2* is a master transcriptional regulator in nervous system development.¹⁶ The resulting impairment is widespread, affecting both speech (physical production of sounds to communicate) and language (comprehension and use of words or symbols to convey meaning).

Regression of acquired speech and language is central to RTT.^{5,17} Children often experience a total loss of verbal expressive ability, including the use of single words and spoken phrases, if acquired at all before regression.¹⁷ Although early forms of communication (e.g. pointing to indicate wants) develop in most individuals with RTT, they are subject to delay.^{17,18} Communication is often mediated through augmentative and alternative communication (AAC) such as eye gaze systems and gesture.^{18–20} Receptive language (comprehension) seems relatively preserved post-regression, although evidence is largely based on caregiver report.^{17,21} Impacts on speech production are not well described; however, atypicalities have been noted including strained or high-pitched vocalizations, and facial muscle weakness which may impact articulation.^{22–26} Impacts are also evident in social communication, or behaviours used for effective interaction. For instance, atypical face scanning in RTT may lead to challenges recognizing emotional expressions.²⁷ People with RTT may also prefer solitude across different variants and stages of regression.²⁸ Overall, communication difficulties are severe, and caregivers report improvement in this domain as the most important symptom to address.^{29,30} Despite this, there is a lack of consolidated data on language development in RTT, and, to our knowledge, no published systematic review of speech–language abilities. A comprehensive analysis is necessary, exploring the acquisition, use, and regression of speech and language across RTT variants.

Profiling speech, language, and social ability in RTT is challenging given the extent of impairment. Traditional assessments often rely on verbal communication, a modality rarely preserved in RTT.^{17,31–33} Many individuals with RTT use AAC systems to communicate; however, motor dysfunction and the loss of volitional control, another defining feature of RTT, may impact the effective use of such technology.¹³ Hence, a restricted ability to respond to assessment questions may be interpreted erroneously as impaired communication, rather than a limitation or suitability of AAC to

What this paper adds

- Verbal expressive ability was most severely impaired across studies, relative to other domains of communication.
- Receptive language showed relative preservation despite severe expressive impairment.
- Strong social motivation persisted despite atypical social profiles.
- Most studies relied on caregiver report rather than direct assessment.
- Objective analysis was facilitated by emerging acoustic/AI models.

Take-home messages

- Severe communication impairment is a hallmark of RTT, affecting speech, language, and social interaction.
- Expressive ability, particularly verbal output, was more severely impaired than receptive language and social communication.
- Communication profiles are modulated by genotype, with certain *MECP2* variants linked to better outcomes.
- Non-verbal modalities, including eye gaze and facial expression, are critical and often under-evaluated forms of communication.
- RTT-specific and multimodal tools are essential, combining objective methods (e.g. eye tracking) with caregiver input.
- Future research must consider longitudinal, prospective design to capture developmental trajectory.

that individual.^{34,35} RTT-specific tools have been established to improve diagnostic accuracy of communication ability.^{36,37} These are often used alongside traditional or adapted assessments, yet there is no ‘criterion standard’ battery for RTT.^{34,38} A systematic review of the primary communication measures in RTT is therefore warranted.

This review aims to (1) describe the speech, language, and social communication phenotype across RTT variants and (2) synthesize and describe the assessments used to measure communication ability in RTT literature.

METHOD

Literature search strategy

Inclusion and exclusion criteria

Eligibility criteria were defined using a PO (Population, Outcome) framework, focused on studies of individuals with

Rett syndrome and reporting speech, language, or social communication outcomes. Screening inclusion criteria were (1) human participants of any age, sex, ethnicity, and geographical location; (2) speech, language, social communication, and/or clinical tools being the primary outcome of investigation OR related to the primary outcome(s); (3) subjective and/or objective report of speech, language, and/or social communication abilities; (4) genetically or clinically confirmed diagnosis of RTT at any stage of progression; (5) direct assessment of patients OR information obtained from caregivers of a person with a confirmed diagnosis of RTT; and (6) publications in any language. For this review, studies considered ‘related to the primary outcome(s)’ were defined as those in which communication abilities were reported as secondary or associated variables in relation to another primary focus (e.g. clinical severity or intervention effects), even where communication was not the principal outcome of investigation. Studies were excluded from full-text analysis if they involved (1) animal studies; (2) participants without confirmed diagnoses of RTT by clinical or genetic report; (3) participants with medical conditions (e.g. acquired brain injury) known to affect speech, language, or social communication; (4) systematic or non-systematic reviews; (5) books or book chapters; and (6) opinion pieces or commentaries.

Studies that included broader populations, but contained results specific to participants with RTT, were also included.

In the present context, communication was defined across three domains: speech, language, and social communication. Speech referred to the physical production of sounds for the purpose of communication, encompassing features such as respiration and articulation. Language referred to the use (expressive) and comprehension (receptive) of symbolic systems to convey meaning, including aspects such as vocabulary and grammar. Social communication referred to behaviours used for effective interaction with other individuals, such as turn-taking.

Primary search

This systematic overview adheres to guidelines established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.³⁹ The review protocol was published and registered at the International Prospective Register of Systematic Reviews (PROSPERO: CRD420251076117) before data extraction. An amendment was made on 23rd February 2026 to update the review's title and author list. An additional amendment was made on 27th May 2026 to reflect both an expanded database search performed during peer review, and the addition of an interrater reliability check for a subset of full-text extractions. Initial searches were conducted on 28th February 2025 in PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and ScienceDirect databases. Expanded database searches were conducted on 11th May 2026 in the Education Resources Information Center (ERIC) and speechBITE databases. The search covered articles from

TABLE 1 Glossary of key terms used in this systematic review.

Search term	Definition
Rett syndrome (RTT)	A neurodevelopmental disorder caused by pathogenic variants of the methyl-CpG-binding protein 2 gene (<i>MECP2</i>), associated with multisystem impairment.
Preserved speech variant (PSV-RTT)	An atypical form of Rett syndrome wherein speech is preserved to varying degrees. Also known as the Zappella variant.
Regression	A period of developmental decline involving the total or partial loss of previously acquired skills, such as purposeful hand use.
Clinical measure	Qualitative or quantitative assessment tool used to measure changes in symptoms, functional capacity, quality of life, and/or any other specified criteria.
Speech	The physical production of sounds for the purpose of communication, encompassing features such as articulation, phonation, and prosody.
Language	The comprehension (i.e. receptive language) and use (i.e. expressive language) of words to convey information.
Social or pragmatic communication	Behaviours used for effective interaction with other individuals, such as turn-taking.
Augmentative and alternative communication (AAC)	Methods of communication used to scaffold or replace verbal speech, such as speech-generating devices or picture boards.

1st January 1985, to 28th February 2025 to capture early descriptive literature following the initial characterization of Rett syndrome. The expanded database searches were restricted to the same timeframe to ensure consistency with the original search strategy and comparability across databases. The full search strings are provided in [Appendix S1](#), as well as a glossary of key terms in [Table 1](#). Search results were exported into Covidence (Veritas Health Innovation Ltd., Melbourne, VIC, Australia, 2025). For the initial search, a preliminary review of titles was conducted by the first author (LNR) to exclude clearly irrelevant articles (e.g. animal studies, studies not involving Rett syndrome, or studies unrelated to communication outcomes). Abstracts were screened independently by two authors (LNR and ROB) to confirm eligibility for full-text analysis. Interrater agreement at this phase was 85.5%. Following peer review, a random subset of full-text articles (20%; $n = 12$) underwent independent verification by a senior author to confirm eligibility decisions and extracted study characteristics. Agreement across the verified subset was 92.6%. If authors did not agree on a paper's inclusion, consensus was achieved through discussion between reviewers with reference to the predefined inclusion and exclusion criteria. Results from the expanded database searches were imported into Covidence and automatically screened for duplicates against records identified in the initial search. Title and abstract screening of newly identified records was subsequently completed by the first author

(LNR). Data extraction was then completed by the first author and reviewed by senior authors.

Supplementary search

A secondary search for clinical trials in RTT was conducted using clinicaltrials.gov. The keywords entered into each search domain are listed here using quotation marks: condition/disease = 'Rett syndrome'; other terms = 'Communication'. Eligibility was not restricted by date of publication, sex, or age, but studies were restricted to 'Interventional' and 'With results'. Trials were restricted to those reporting results to allow synthesis of outcome measures, rather than protocol-only registrations.

Quality appraisal

For papers included in the full-text review, a quality appraisal was performed using the JBI Critical Appraisal Tools. Given the inclusion of various study types, six different JBI tools were required.^{40–43} Papers were stratified according to their type and analysed using the relevant JBI checklist. For studies using hybrid or atypical designs, the closest-fitting checklist was applied. Items that were not applicable were recorded as such and excluded from domain judgements. Quality appraisal was completed by the first author and reviewed by senior authors. Studies were not excluded on the basis of appraisal outcomes alone; instead, appraisal findings were used to inform interpretation of methodological limitations and strength of evidence during narrative synthesis. Results of this analysis are presented in [Appendix S2](#).

Data synthesis

Data extraction and synthesis were completed by the first author (a speech–language pathologist). Findings were synthesized narratively by domain (speech production, language features, social communication), with subgroup patterns (e.g. classic RTT vs PSV-RTT) extracted where possible. Outcome measures were tabulated according to their domain of communication, mode of administration, and frequency in the literature. Statistical comparison was not feasible due to heterogeneity in methods and results.

RESULTS

A total of 3091 records were identified through database searches after the removal of duplicates. Two hundred and twenty-five records were retained following title screening. After abstract screening, 64 records were eligible for full-text review. Reasons for exclusion at full-text review were the inclusion of participants without a diagnosis of RTT confirmed by clinical or genetic report ($n = 4$), and article type

(non-systematic review; $n = 1$). A critical summary of the remaining 59 papers is provided below, categorized according to domains of communication: speech (physical production of sounds), language (use and comprehension of words and symbols to convey meaning), social communication (behaviours used for effective interaction with other individuals), and clinical outcome assessments. The study selection process is presented in [Figure S5](#); all included papers are listed in [Appendix S3](#). Studies contributing to the synthesis consisted primarily of observational studies, including cross-sectional analyses, case series, and case reports, with fewer quasi-experimental studies and one randomized controlled trial. The evidence base was predominantly retrospective, caregiver-reported, and based on small samples ([Figure 1](#)). Approximately one-fifth of the studies involved retrospective video analysis.

The supplementary search of clinicaltrials.gov yielded seven records. Screening of study overviews was conducted by the primary author (LNR). Two studies were removed: one was a duplicate, and one did not provide outcome measure data. The remaining five trials are summarized according to the clinical outcome assessments used and results of therapeutic intervention in the sections on 'Communication measures used in RTT drug trials (supplementary search)' and 'Interventional approaches' respectively.

Speech production

Pre-regression development

Pre-linguistic vocal development in RTT differed from typical trajectories. Four retrospective analyses (total $n = 8$; age range: 6–24 months) described intermittent patterns of typical and atypical vocalizations, across both RTT and PSV-RTT, emerging from about 6 months.^{23,44–46} Atypicality was characterized by inhalatory, pressed, high-pitched and crying-like qualities, extremely short inhalation periods, breathiness, and irregular respiratory cycling.^{23,44–46} Detailed case work in PSV-RTT confirmed these deviations in timbre, rhythm, and pitch between 7 months and 12 months of age; objective analysis revealed pressed phonation and irregular respiration.²³ Spectral and temporal differences were robust enough that, using automated analysis, RTT and typically developing vocalizations could be discriminated with up to 98.3% classification performance; timbre and frequency features were most salient.²² Together, these data suggested that acoustic-perceptual anomalies may emerge before regression. It should be noted that studies describing the period between late infancy and regression (i.e. ~12–18 months) were limited.

Canonical babbling (the production of well-formed, speech-like sounds) milestones were variably achieved. Generally, canonical babbling is a strong predictor of downstream speech acquisition.^{47,48} In a small pre-regression comparison ($n = 3$; age range: 9–11 months), all infants reached canonical babbling by 9 months; however, those later diagnosed with RTT showed lower canonical babbling ratios overall, and fewer pre-linguistic

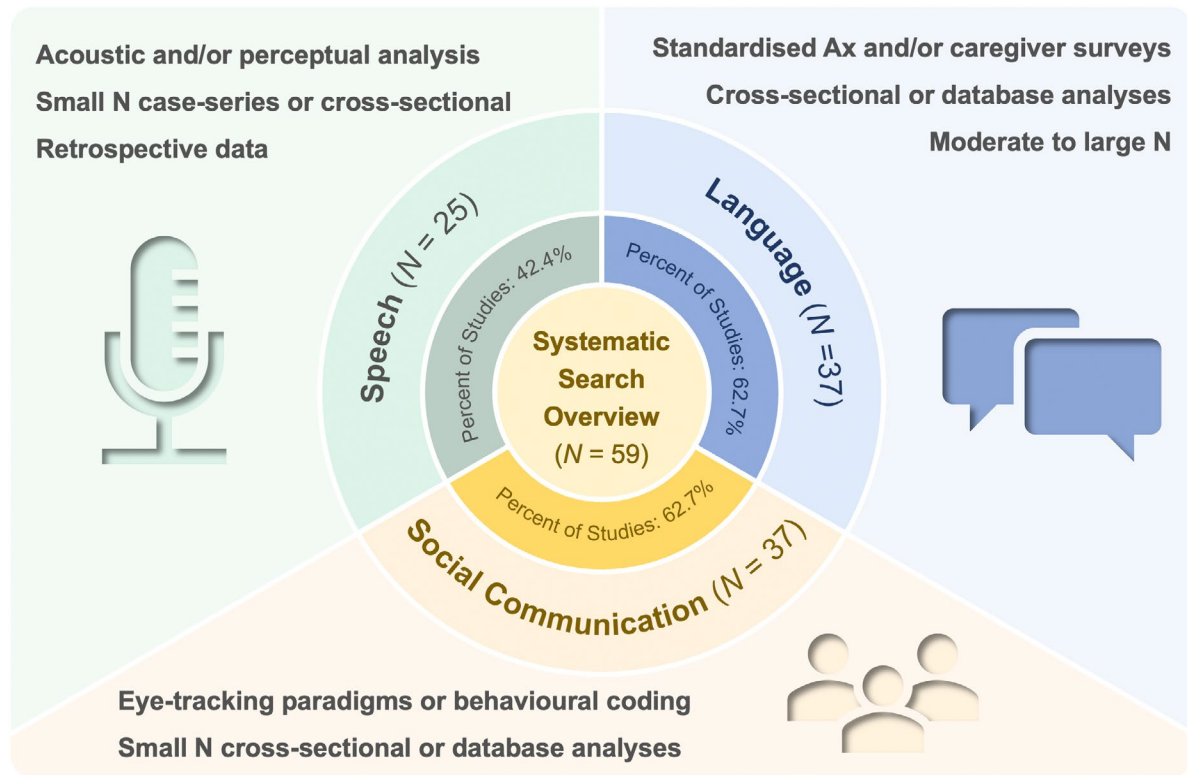


FIGURE 1 Overview of systematic search results. Percentages do not sum to 100% owing to categorization of studies across multiple communication domains. Abbreviation: Ax, assessment.

vocalizations.⁴⁹ In the same study, a strong reduction in canonical babbling ratios was observed in one female with RTT.⁴⁹ Another cohort reported typical babbling onset in all participants ($n = 8$ out of 8) before regression.⁵⁰ By contrast, two other retrospective video studies reported absent canonical and/or variegated babble in a varying number of cases (study 1: $n = 6$ out of 6; study 2: $n = 2$ out of 6; total age range: 7–24 months).^{19,44} The inconsistent achievement of babbling milestones was supported by dataset analyses of caregiver-reported data. In a study of 766 individuals, 10.6% ($n = 81$) acquired no speech–language ability pre-regression, whereby the median age at regression was 18 months (age range: 4 months–7 years 6 months); of those who did develop some speech or language pre-regression ($n = 545$), babble was the highest level achieved in 22.6% ($n = 123$).⁵¹ In a later cohort, 27.9% ($n = 38$ out of 136) achieved neither babble nor words, while 55.9% ($n = 76$ out of 136) reached babble.⁵² Overall, pre-regression anomalies spanned both acoustic (i.e. voice quality, respiration, spectral structure) and phonetic (i.e. syllabicity, canonical babbling ratio) domains.

Regression patterns and impacts

The timing and severity of speech regression in RTT were heterogenous and not necessarily aligned with an individual's global regression. Median age at speech loss ranged from 18 months to 24 months, with an overall window of 4 months to 7 years 6 months.^{45,50,51,53–56} Among individuals with previous speech–language ability, 84.8% ($n = 581$ out of 685)

regressed in one database cohort.⁵¹ Stratification by *MECP2* status revealed a gradient: speech–language regression occurred in 98.7% to 100% of *MECP2*-positive cases, versus 46.2% to 87.8% of atypical (including *MECP2*-negative) cases across cohorts.^{57–59} These differences probably implicated the type and severity of genetic variation, which are discussed in the section on ‘Variation across *MECP2* genotypes’.

In cases where speech was retained or recovered following regression, acoustic-perceptual anomalies were common. Respiratory disturbances including hyperventilation, apnoea, aerophagia, and irregular rhythm occurred in 31.3% to 79.5% of *MECP2*-positive samples, and were also described in PSV-RTT.^{46,50,55,57,60–62} Prosodic anomalies included rapid speech rate, fragmentation, soft or breathless voice, and persistent high pitch.^{58,63} Even with lexical improvement in PSV-RTT, speech was marked by idiosyncratic vocalizations and rhythmic prosodic events; articulation was also limited in accuracy.^{45,46} None of the included studies prospectively assessed speech disorders (e.g. dysarthria or childhood apraxia of speech), given the severity of speech loss observed in most cases.

Language

Expressive and receptive language

Pre-regression development

Pre-regression communication was often characterized by use of non-verbal modalities, including gesture,

body movements, facial expressions, and non-linguistic vocalizations.^{19,45,50,64–66} Four studies (total $n = 14$; age range: 6–24 months) categorized early behaviours using the Inventory of Potential Communicative Acts.^{19,45,64,65} Gestural repertoires were small, ranging from zero to six gestures per child, and largely deictic (e.g. pointing at an object) rather than representational (e.g. pretending to brush hair). Behaviours were repetitive, contextually inappropriate, and delayed in response.^{45,65,66} Between three and eight communicative functions were observed per child, with requesting and attention-directing most common. Notably, choice-making functions (e.g. pointing or vocalizing to choose between two alternatives) were absent across cohorts.^{19,45,64–66}

Expressive language ability varied across studies. In a database analysis of 766 females with RTT, the highest level of language attained before regression (median age at regression = 18 months) was use of one or more words in 77.4% and babble in 22.6%.⁵¹ In a caregiver cohort of 125 females, 68.9% used one or more words, and 12.3% used sentences.⁵⁵ In a birth cohort of six females, none of the RTT cases attained 10 verbal words or produced word combinations by 18 months.⁶⁷ By contrast, another study reported that two females with classic RTT acquired vocabularies of approximately 10 words before regression, occurring at 15 and 18 months respectively.⁵⁰ PSV-RTT (total $n = 13$; age range: 6–24 months) showed comparatively stronger early verbal profiles, including the use of proto-words (e.g. <efant> for <elephant>), and achievement of first words within a typical milestone range; however, reduced verbal output, verbal perseveration, and vocabulary restricted to mainly nouns and predicates, persisted.^{44–46,64,65}

Direct assessment of pre-regression receptive ability was scarce. However, orienting to name and responding to familiar acoustic stimuli were common, implying capacity; authors contended that non-response may reflect features of other comorbidities such as autism spectrum disorder.^{19,65,67} In this context, orienting to name can also be interpreted as a marker of receptive language ability (i.e. comprehension of one's own name).

Regression patterns and impacts

Non-verbal modalities became central to communication following regression. Eye gaze was the most consistent intentional modality.^{21,52,55,57,68,69} Eye-pointing or back-and-forth glancing were used to request, make choices, direct attention, and respond 'yes' or 'no' in up to 98.3% ($n = 59$ out of 60) of MECP2-positive cases.⁵⁷ A large cohort study ($n = 151$) collated items related to eye gaze from the Communication and Symbolic Behavior Scales (CSBS).⁵² Higher scores indicated a greater frequency of communicative eye gaze behaviours. Mean eye gaze scores decreased modestly from adolescence (13 to <19 years: mean = 4.21, SD = 1.26; $n = 29$) to adulthood (>19 years: mean = 3.34, SD = 1.35; $n = 53$).⁵² Body movements and gesture (e.g. pointing) were used by up to 90% to express will, but conventional gestures such as waving or beckoning were rare.^{45,50,55,68,70–72} CSBS gesture scores were low on average (mean = 1.46 out of 10, SD = 1.96; $n = 151$), and tended to be stronger in younger or more

mobile participants.⁵² Gesture was also constrained by repetitive hand stereotypies, present in 37.5% pre-diagnosis, and 79.2% at the time of genetic testing, with onset as early as 6.5 months.^{44,46,73} Post-regression, hand stereotypies were almost universal.^{45,46,50,54,57,59,61–63,74–79} Recovery of gesture was seen in one case of PSV-RTT.⁴⁵ Facial expressions conveyed rich emotion but could be erratic.⁴⁵ Overall, non-verbal intentionality often remained at preintentional or perlocutionary levels.^{21,52,80}

Verbal expressive ability post-regression often manifested as isolated words or approximations in classic RTT.^{21,54,68,70} Atypical RTT forms showed more advanced profiles: in one subgroup ($n = 13$; mean = 22 years 5 months, SD = 8 years 7 months), 46.2% used sentences, 30.8% phrases, 15.4% single words, and 7.7% parts of words.⁵⁸ Two females with the milder forme fruste variant demonstrated speech recovery at 7 years and between 8 years and 9 years respectively.⁵⁰ One longitudinal PSV-RTT case documented growth from 15 words between 3 years and 6 years, to word combinations and correct pronoun use between 6 years and 11 years.⁴⁵ More broadly, however, echolalia and morphosyntactic/phonological errors persisted.^{21,45,46,53,63} Standardized assessments quantified this impairment. Across studies, individual Vineland Adaptive Behavior Scales (VABS) communication standard scores ranged between 1.5 and 73.7; this is consistent with low to moderately low functioning.^{54,77,81} In another study, age equivalents for VABS expressive language ranged from 1 to 38 months among participants aged 11 to 36 years (mean = 23 years).⁵⁰ An RTT-specific verbal scale (RTT-VCOM) also showed moderate to severe language impairment across a large cohort ($n = 187$).⁸² Vocalizations were often used communicatively (e.g. for gaining attention, protesting or requesting more). In one caregiver study ($n = 125$; age range: 2 years 6 months–55 years), 55% of respondents ($n = 55$ out of 100) used vocal sounds to express will; three other papers described idiosyncratic mappings of vocal forms to meanings (total $n = 20$; age range: 2–55 years).^{21,55,56,70} In one case of classic RTT, researchers showed that unconventional vocalizations were specifically used to indicate 'yes' and 'no', and carried distinct spectral and temporal patterns.⁵⁶

Receptive language demonstrated greater resilience than expressive post-regression. Findings were derived largely from caregiver report and indirect measures. In classic RTT, standardized scores for receptive ability often surpassed expressive ability.^{50,62,69} Across participants (total $n = 68$; age range: 2–51 years), yes/no comprehension was often demonstrated through gaze, vocalizations, or symbol selection using AAC, with a weaker understanding of abstract symbols (e.g. illustrations) compared with concrete ones (e.g. photographs).^{21,56,68,71} However, these outcomes may have been influenced by methodological factors. While social composite scores, which include items on receptive ability (e.g. understanding gestures such as pointing), were low on the CSBS Developmental Profile Infant-Toddler Checklist (mean = 8.8 out of 26, SD = 3.27, $n = 187$), eye-tracking studies showed active attention to objects named out loud; however, fixation declined across trials.^{62,82,83} Higher clinical severity predicted

lower receptive scores on the Mullen Scales of Early Learning ($\beta = -0.26$, $p = 0.001$).⁶² In atypical RTT, 84.6% understood sentence-level speech, and 53.8% demonstrated reading ability; one ($n = 1$ out of 13) individual was reported to read novels.⁵⁸

Social communication

Pre-regression development

Early atypicality was evident in the RTT social profile. In 10 females with classic RTT, retrospective video analysis showed participants orienting to their name (e.g. by turning their head when their name was called) in 38.1% of instances between 5 months and 8 months, falling to 12.5% between 19 months and 24 months.⁸⁴ This skill increased in the PSV-RTT group, with orientation to name observed in 27% to 42.6% of instances across the same timeframe.⁸⁴

However, in another cohort of six females with classic RTT, orientation to name was observed in 100% of participants between 9 months and 12 months.¹⁹ Seventy-five per cent of mothers reported that their child did not try to gain adults' attention when left alone.⁸⁵ Autistic features were also described in early communicative patterns.^{19,45,46,65,66} A shift towards perseveration or echolalia manifested within the second year, namely in PSV-RTT.^{45,46,65,66}

Regression patterns and impacts

Following regression, a unique pattern of socio-communicative behaviour emerged alongside high social motivation. Eye-tracking studies (total $n = 86$; age range: 1 year 6 months–31 years) showed preferential gaze to people and socially relevant facial regions over objects.^{27,86} In complex scenes, 74% of fixations were to people, and while observing static faces, 68% of viewing time was on the eyes.⁸⁶ However, the overall time spent observing facial features, as well as the number of fixations, were lower in RTT than typically developing groups.²⁷ Fixation metrics also varied with age, clinical severity, and stimulus familiarity; for example, participants looked longer at teachers than peers in a virtual classroom.^{27,75,86} On the Early Social Communication Scales, younger participants (i.e. ≤ 10 years; $n = 14$) showed more frequent eye contact and alternating gaze than older ones (i.e. 11–18 years; $n = 15$), and poorer scores correlated with increasing clinical severity ($\beta \approx -0.23$ to -0.03).⁶²

Caregiver reports and standardized measures suggested a unique social profile.^{62,77,87,88} In one cohort of 57 participants, the mean VABS socialization domain score was 19.7 (SD = 12.2; range: 3.4–50.0).⁷⁷ Age also predicted a decline in VABS socialization ($r^2 = 0.57$), although caregiver-rated scores on the Screen for Social Interaction remained stable.⁷⁷

Autistic behaviours were frequently reported. Diagnostic overlap with autism spectrum disorder was common in early development, with one cohort ($n = 24$) receiving referrals to psychiatry in 29.2%, and provisional diagnoses of autism spectrum disorder before *MECP2* testing in 8.3%.⁷³ In another series ($n = 52$), 76.8% had a previous diagnosis

of childhood autism; yet at reassessment, 19.2% no longer met criteria (predominantly those aged ≥ 10 years), while 42.3% to 57.7% still met diagnostic criteria for autism spectrum disorder.⁷⁹ Behavioural heterogeneity was wide, from reduced social engagement and a preference for solitude, to clear reciprocity, initiation, and peer interest.^{55,77,79,87,89,90} Facial expressions were often idiosyncratic or limited. In response to music, 'activating' songs evoked the highest count of smiles ($n = 15$ out of 34 total expressions), and unfamiliar music the most expressions of disgust ($n = 20$ out of 31).⁹¹ Just over half (51.7%) of the same cohort showed idiosyncratic facial actions irrespective of stimulus, as reflected in other studies; authors contended that this could reflect abnormal spontaneous brainstem activation.^{46,64,77,90–92} Emotional lability was also common. Parents reported an increase in the frequency of socio-emotional behaviours (e.g. crying) after stage II of RTT, measured using an adaptation of the Screen for Social Interaction (mean = 1.99–2.55; $t_{50} = -8.67$, $p < 0.001$).⁸⁹ Mood swings were reported by 58.3% to 62% of caregivers, with laughter or screaming spells in 50% to 100% of females across typical and atypical RTT.^{50,57,79,92} Emotional dysregulation and anxiety were frequently noted after regression.^{45,46,57,59,63,71,74,79,81,89,90,92,93}

Variation across *MECP2* genotypes

Genotype modulated communication abilities along a broad continuum. However, many genotype–phenotype associations were derived from small cohorts and case-based evidence. Frameshift and early truncating variants (e.g. c.1163del44; p.Arg168*) were generally associated with absent or limited speech, whereas missense variants such as p.Arg133Cys and p.Arg306Cys were linked to milder outcomes; these include delayed but present babbling, or partial speech recovery.^{45,46,54,57,59,61–63,74–79} Among a small subgroup of participants who used conversational language, p.Arg133Cys and carboxy (C)-terminal deletions each accounted for 38.5% ($n = 5$ out of 13) of cases.⁵⁸ Outliers emphasized the role of modifiers: unusually high canonical babbling ratios and target-language vocalizations have been reported in one case of p.Arg168*;⁴⁹ similarly, early speech-like behaviours were preserved despite a large intragenic deletion (c.378-43_964delinsGA) in a case of PSV-RTT.⁴⁶ Favourable X-chromosome inactivation patterns were considered plausible contributors to milder phenotypes.⁵⁸ Retention of single words post-regression was more likely with milder variants such as p.Arg133Cys and C-terminal deletions, relative to early truncations and large deletions.^{45,46,54,63,74} The relative risk ratio for word retention in those with p.Arg133Cys mutations was 3.45 pre-regression (95% CI = 1.15–10.41), and 5.99 post-regression (95% CI = 2.00–17.92).⁵¹ Comparative work places p.Arg133Cys at the milder end, relative to p.Pro152Arg and p.Thr158Met.⁷⁶ Use of eye gaze for communication was present across *MECP2* variants (98.3%; $n = 59$ out of 60), but use of gesture to communicate was significantly higher with C-terminal

deletions and p.Arg133Cys variants than early truncations and larger deletions.^{52,57}

Receptive language outcomes by genotype were explored less systematically. Nevertheless, non-classic genotypes (e.g. late C-terminal changes) more often exhibited sentence-level comprehension and literacy than truncating variants.⁵⁸

Evidence linking pragmatic ability and genotype was also scarce, only reported in nine studies. Early autistic behaviours or sudden social withdrawal were described across individuals with early truncations (e.g. p.Gln128*, p.Arg168*, p.Arg270*), C-terminal deletions (e.g. c.1155del12, c.1163del35, c.1164del44), and missense variants (e.g. p.Phe157Leu, p.Thr158Met).⁷³ Individuals with *MECP2*-positive forms showed more pronounced early stereotypy and social withdrawal than those with atypical forms.⁶¹ In a cohort of 80 females, associations differed by instrument: on the Screen for Social Interaction, lower scores were reported for p.Arg106Trp, p.Arg133Cys, p.Arg168*, p.Arg255*, and p.Arg294*.⁷⁷ On VABS Socialization, p.Arg133Cys and p.Arg270* showed relatively higher means, and p.Arg106Trp and p.Thr158Met the lowest.⁷⁷ Some pairwise contrasts were significant: p.Arg133Cys versus p.Arg106Trp ($p = 0.025$, $z = 2.245$, $r = 0.6$),

and p.Arg133Cys versus p.Thr158Met ($p = 0.0491$, $z = 1.967$, $r = 0.5$).⁷⁷ Case reports aligned with these gradients; p.Arg133Cys was linked to milder language impairment, but also emotional dysregulation and unusual facial expressions; large intragenic deletions were accompanied by persistent autistic features; and p.Arg306* was linked to autistic regression.^{45,46,54,63,74} Across variants, behaviours of affiliation (e.g. humour and affection) were generally present, although distress triggers varied.⁵⁸ Overall, genotype seemed to modulate social profiles, but findings must be interpreted cautiously.

Clinical outcome measures

Overview of clinical measures

Given the speech–language difficulties in RTT, many studies (62.7%; $n = 37$ out of 59) relied on caregiver-reported measures of communication. The most commonly reported measures of speech, language, and/or social ability are summarized in Table 2, as well as their relative frequency, domains of communication, and mode of administration.

TABLE 2 Most commonly reported communication measures in Rett syndrome (RTT) literature (primary search).

Endpoint	Frequency (n out of 59)	Communication features assessed	Mode of administration
Retrospective video analysis	20.3% ($n = 12$)	- Speech production - Receptive language - Verbal expressive language - Non-verbal expressive language - Social communication	Observational analysis of existing footage coded by researchers
Vineland Adaptive Behavior Scales (VABS) ¹¹³	16.9% ($n = 10$)	- Receptive language - Verbal expressive language - Non-verbal expressive language - Social communication	- Caregiver or teacher questionnaire - Semi-structured interview
Eye-tracking paradigm	11.9% ($n = 7$)	- Receptive language - Verbal expressive language - Social communication	- Eye-tracking device (e.g. Tobii Pro X3-120) - Eye-tracking software (e.g. Tobii Pro Lab Full Edition)
Inventory of Potential Communicative Acts (IPCA) ¹¹⁴	8.5% ($n = 5$)	- Non-verbal expressive language - Social communication	- Caregiver or teacher questionnaire - Semi-structured interview
Clinical Severity Scale (CSS or RTT-CSS) ¹¹⁵	8.5% ($n = 5$)	- Speech production - Verbal expressive ability - Non-verbal expressive ability	- Clinician rating - Caregiver or teacher questionnaire
Acoustic analysis	5.1% ($n = 3$)	Speech production	Acoustic signal processing software (e.g. openSMILE)
MacArthur-Bates Communicative Development Inventories (or adaptations; MB-CDI) ¹¹⁶	5.1% ($n = 3$)	- Receptive language - Verbal expressive language - Non-verbal expressive language	- Caregiver or teacher questionnaire - Semi-structured interview
Communication Matrix (CM) ¹¹⁷	5.1% ($n = 3$)	- Verbal expressive language - Non-verbal expressive language	- Caregiver or teacher questionnaire - Semi-structured interview
Communication and Symbolic Behavior Scales (CSBS) ¹¹⁸	5.1% ($n = 3$)	- Speech production - Receptive language - Verbal expressive language - Non-verbal expressive language - Social communication	- Caregiver or teacher questionnaire - Semi-structured interview
Kerr Scale ¹¹⁹	5.1% ($n = 3$)	- Speech production - Verbal expressive language - Social communication	- Clinician rating - Semi-structured interview

A comprehensive list of all communication-related measures and techniques, and the studies administering them, is provided in [Appendix S4](#). Several RTT-specific measures were also identified, including the Observer-Reported Communication Ability measure adapted for RTT (ORCA-RTT), RTT Ability to Communicate Choices (RTT-COMC), and Rett Assessment Rating Scales, although these varied in their specificity to communication outcomes.

Communication measures used in RTT drug trials (supplementary search)

Clinical trials in RTT often involved a communication assessment. Use of caregiver questionnaires was ubiquitous due to the nature of impairment. Of the included studies, 100% ($n = 5$ out of 5) involved at least one caregiver-reported communication measure. All assessments containing a speech, language, and/or social ability component are summarized in [Table 3](#), as well as their relative frequency, domains of communication, and mode of administration.

Interventional approaches

Eight studies from the primary search (13.6%) described interventions involving communication outcomes, spanning AAC, physiological approaches, and behavioural therapies.^{54,70,71,81,82,88,94}

AAC interventions were associated with communication improvements in small RTT samples using both low-tech (e.g. laminated symbols) and high-tech (e.g. Proloquo2Go) systems.^{70,71} In one study, all three participants learned to request with both low and high-tech systems, reaching mastery after 6 to 54 sessions (high-tech) and 16 to 52 sessions (low-tech), with independent request gains of 1.55 to 3.33 (high-tech) and 3.10 to 3.44 (low-tech).⁷⁰ Similar gains were observed using a computer-based requesting system with animated graphics; requesting behaviours increased in three females (age range: 5 years 2 months–11 years 7 months), with two meeting acquisition criteria for all target lexigrams, and successful generalization across settings.⁹⁵ Complementary partner-mediated strategies were also beneficial. For instance, aided language modelling, where a communication partner models language by simultaneously speaking and pointing to symbols on an AAC system, was associated with an increase in independently produced words per minute over 6 weeks (Tau-U = 0.68, 0.69, 0.74) and moderate-to-large gains in overall words per minute (Tau-U = 0.21, 0.25, 0.49).⁷¹

Preliminary evidence supported communication-related changes following neuromodulatory treatment. When combined with linguistic training, transcranial direct current stimulation over Broca's area increased vowels/consonants, words, and comprehension in three females, alongside neurophysiological changes (alpha 8.1 Hz to 8.6 Hz; beta 14.2 Hz to 19.4 Hz; theta 4.7 Hz to 7.3 Hz).⁵⁴

Behavioural programmes were also associated with improvements in several communication domains. A 24-week

TABLE 3 All reported communication measures in Rett syndrome (RTT) clinical trials (supplementary search).

Endpoint	Frequency (n out of 5)	Communication features assessed	Mode of administration	Study
Anxiety, Depression, and Mood Scale (ADAMS) ¹²⁰	40% ($n = 2$)	Social communication	Caregiver or teacher questionnaire	94,99
Communication and Symbolic Behavior Scales (CSBS) ¹¹⁸	40% ($n = 2$)	- Speech production - Receptive language - Verbal expressive language - Non-verbal expressive language - Social communication	- Caregiver or teacher questionnaire - Semi-structured interview	94,102
Mullen Scales of Early Learning (MSEL) ¹²¹	40% ($n = 2$)	- Receptive language - Verbal expressive language - Non-verbal expressive language	Clinician rating	94,100
Vineland Adaptive Behavior Scales (VABS) ¹¹³	40% ($n = 2$)	- Receptive language - Verbal expressive language - Non-verbal expressive language - Social communication	- Caregiver or teacher questionnaire - Semi-structured interview	94,100
RTT Ability to Communicate Choices (RTT-COMC) ^{82,102}	20% ($n = 1$)	Non-verbal expressive language	Clinician rating	102
Kerr Scale ¹¹⁹	20% ($n = 1$)	- Speech production - Verbal expressive language - Social communication	- Clinician rating - Semi-structured interview	94
Screen for Social Interaction ¹²²	20% ($n = 1$)	Social communication	- Caregiver or teacher questionnaire - Semi-structured interview	100
Caregiver-Rated Impression of Change (CIC) ¹⁰¹	20% ($n = 1$)	- Verbal expressive language - Non-verbal expressive language - Social communication	Caregiver questionnaire	101

music therapy protocol (two 120-minute sessions/week) improved multiple outcomes relative to controls: VABS Receptive (7.36 [2.42] vs 4.17 [2.86], $p < 0.05$), VABS Socialization (7.45 [2.58] vs 3.17 [4.80], $p < 0.01$), reduced clinical severity on the RCSS (4.82 [2.23] vs 6.50 [1.88], $p < 0.05$), improved language function on the RCSS (0.91 [0.54] vs 1.50 [0.52], $p < 0.05$), and increased eye-gaze duration (216.36 s [188.06 s] vs 49.55 s [81.22 s], $p < .005$).⁸¹ Early intensive behavioural intervention (applied behavior analysis-based) was applied to identical twins with RTT for 33 months and produced VABS gains of +31 and +33 (communication), +3 and +3 (daily living), and +20 and +23 (socialization); age equivalents for these increases are ~8 months and 10 months, 2 months and 8 months, and 10 months and 9 months respectively.⁸⁸ However, Adaptive Behavior Composite scores declined slightly from 52 to 48, and 49 to 48. The Assessment of Basic Language and Learning Skills - Revised showed social interaction improvements of 38% and 33%.⁹⁶

Pharmacological interventions produced mixed findings. Trofinetide produced nominal, statistically significant improvements over placebo in a secondary endpoint analysis on the parent-reported CSBS Developmental Profile Infant-Toddler Checklist social composite (least squares mean difference = 1.0; Cohen's $d = 0.43$) and on RTT-COMC (non-verbal communication; least squares mean difference = 0.3; $d = 0.36$), with no effect on RTT-VCOM (verbal communication).^{82,97} These scale-level changes were not judged by the US Food and Drug Administration to support a communication-related claim in the prescribing information.⁹⁸ The supplementary

pharmacological search, limited to those including communication assessment, also produced mixed results. Four agents were identified: rhIGF-1, dextromethorphan, sarizotan, and trofinetide, although programmes were discontinued because of lack of efficacy, and none have received regulatory approval other than trofinetide.^{94,99–102} These trials attempted to assess communication ability by means of the Anxiety, Depression, and Mood Scale; Social Avoidance Scale; Mullen Scales of Early Learning Expressive Language; Caregiver CIC, VABS, CSBS-DP, RTT-COMC, and RTT-VCOM with variable results (see [Appendix S4](#) for acronym definitions). Effects on social and non-verbal measures seemed more consistent than verbal outcomes. Larger controlled datasets are necessary before recommending agents to remediate speech–language impairments in RTT. Taken together, pharmacological findings show mixed changes in communication ability, suggesting objective measures could be useful in systematic speech–language assessment.

Overall, preliminary evidence from small and heterogeneous studies suggested potential improvements in communication outcomes.^{54,70,71,81,82,88}

DISCUSSION

This systematic review collated evidence on communication phenotypes in RTT, detailing speech, language, and social ability across *MECP2* variants ([Figure 2](#)). We highlight the foremost clinical measures used in RTT research, both pre- and post-regression. To our knowledge, this is the first paper

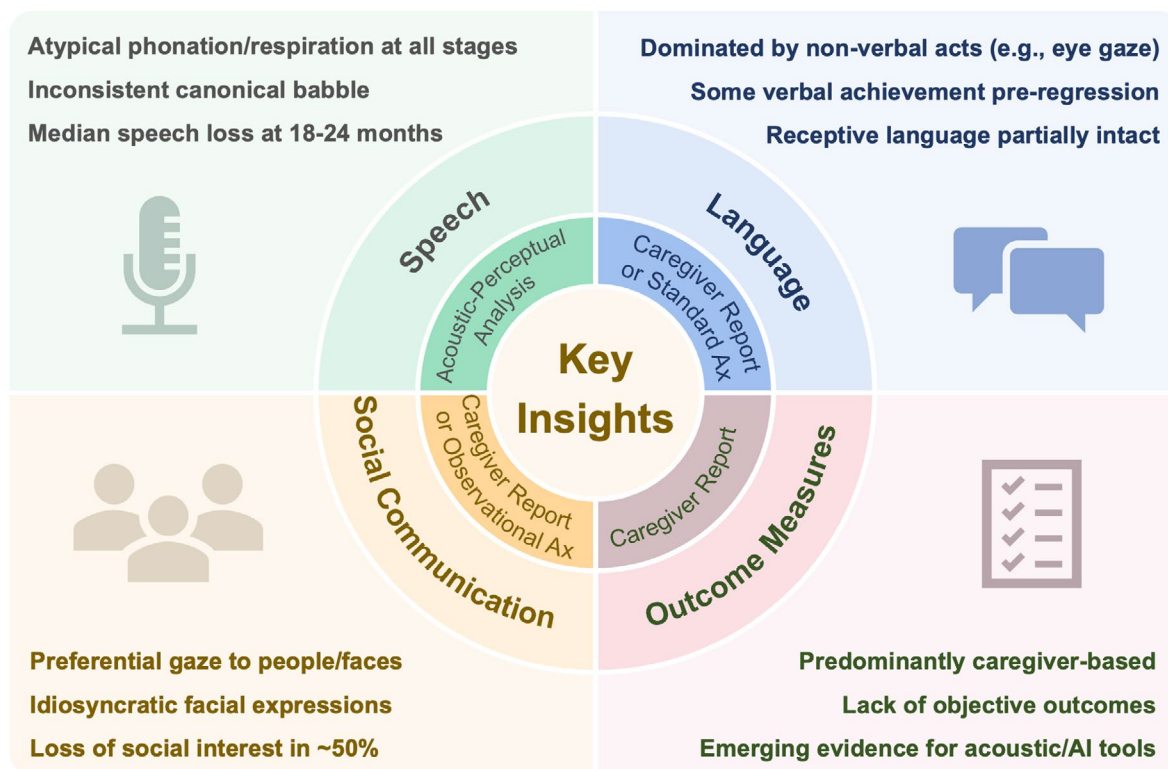


FIGURE 2 Key insights from the current systematic review. Abbreviation: Ax, assessment.

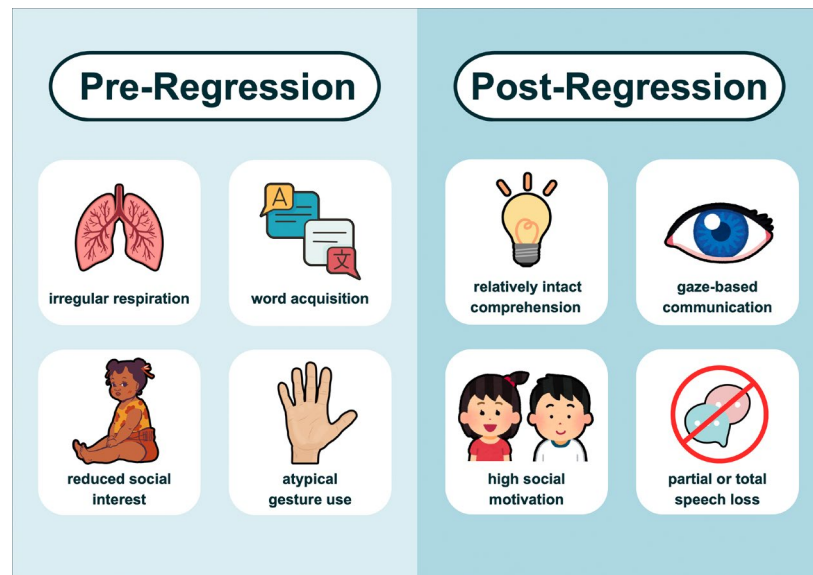


FIGURE 3 Pre- versus post-regression communication phenotypes in Rett syndrome.

characterizing communication ability in RTT systematically. Fifty-nine publications were examined. Owing to the nature of communication impairment in RTT, many of the included studies relied on caregiver recall and observational analysis. The available evidence highlights a broad spectrum of communication ability, modulated by genotype, age, clinical severity, and RTT subtype. Further, pre- and post-regression phenotypes are discrete across all areas (Figure 3).

Speech

Impairments in physical speech production are common across RTT, evident from infancy and through regression. Numerous studies ($n = 12$; 20.3%) used retrospective analysis of home audio-video recordings made pre-diagnosis. Pre-regression findings show atypical vocalization in both acoustic and perceptual domains, including high pitch and breathiness.^{23,44–46} During regression, individuals lose acquired speech, typically between 18 months and 24 months of age.^{45,51,53–56} However, the timing and severity of regression are highly variable, influenced by genotype and RTT subtype.^{44,53} Post-regression speech often shows disordered features, including hyperventilation and high pitch, even among those who retain verbal ability.^{45,46} While missense *MECP2* variants (e.g. p.Arg133Cys) are associated with milder impairments, speech disruption is almost ubiquitous in RTT.^{44,53} Oral speech production is therefore an unreliable mode of communication for most individuals with RTT.

Expressive and receptive language

Marked impacts on language are evident in RTT, namely expressive ability. Pre-regression, some children demonstrate

the use of single words or proto-words (word-like utterances).^{50,51,55} A small percentage (12.3%) exhibit sentence-level speech, mainly in atypical forms such as PSV-RTT.⁵⁵ Overall, verbal output is limited, characterized by reduced lexical diversity and perseveration.^{19,44,45,64,65} Following regression, most individuals retain non-verbal forms of expression (e.g. eye gaze and/or gesture).^{21,50,52,55,57,68,69} In contrast, receptive language tends to be more preserved; many demonstrate an understanding of names, instructions, and familiar words.^{50,58,62,69} Comprehension is often context-bound, and varies across individuals. These outcomes are also shaped by genetic variation. Milder *MECP2* mutations (e.g. p.Arg133Cys) are linked to better-preserved language abilities.⁵¹

Social communication

The social profile in RTT is somewhat paradoxical. Differences in social ability are often seen alongside a preference for social stimuli.^{27,86} Pre-regression, children demonstrate reduced social orienting and limited gestural repertoires relative to typically developing peers.^{19,84} Post-regression, however, interest in human faces and emotional reciprocity is preserved, as confirmed by eye-tracking and caregiver reports.^{27,86} This is particularly the case among younger individuals. However, idiosyncratic facial expressions due to brainstem dysfunction, as well as motor stereotypies such as hand-wringing, may limit social signalling.⁹¹ Mood lability, spells of laughter or screaming, and fluctuating autistic traits are common, but often attenuate with age.^{46,50,64,77,90–92} *MECP2* variants again may modulate social development, although the evidence is limited and warrants further study.^{45,46,54,61,63,73,74,77}

Clinical outcome measures

Communication assessment in RTT is limited by speech and motor impairments, leading to a reliance on caregiver report and adapted tools.^{37,72,103–106} The most common prospective assessment was analysis of home video recordings.^{19,22,23,44–46,49,50,64–66,84} The assessment tools used most frequently were the VABS and the Inventory of Potential Communicative Acts. Eye-tracking paradigms and RTT-specific tools (e.g. RTT-COMC) may offer greater nuance around communicative ability, due to reduced motor demands and increased sensitivity to subtle gaze-based and non-verbal behaviours.^{27,82,86,94} Outcome scores on all assessments were significantly impacted by age, clinical severity, genotype, and RTT subtype. This highlights the need for flexible and RTT-sensitive measures, across both clinical and research environments. To date, only the Observer-Reported Communication Ability Measure has been developed to assess communication strategies in primarily non-verbal neurodevelopmental disorders, according to the US Food and Drug Administration regulatory standards for individuals with Angelman syndrome, and includes expansion into other neurodevelopmental disorders.¹⁰⁷ A version of the Observer-Reported Communication Ability Measure has been developed to assess non-verbal communication abilities in individuals with RTT.³⁷

Pharmacological trials

Few pharmaceutical trials have investigated the effects of therapeutic agents on communication in RTT. Of the five studies identified through clinicaltrials.gov, most assessed clinical efficacy, with only secondary attention to speech-language changes. Trofinetide was most extensively studied; trials reported modest improvements in caregiver-rated measures of communication and social engagement.^{82,102} However, these findings were based on subjective endpoints. Direct speech-language assessment was rare. Other agents such as sarizotan were trialled, occasionally noting anecdotal improvements in communication.¹⁰¹ Overall, trials with pharmacological interventions show that communication-specific improvements are inconsistently measured and poorly quantified. Scales are often inappropriate for a predominantly non-verbal population, are likely to show floor effects, and contain questions that are not applicable for individuals with RTT. Greater robustness and domain-specific measures are necessary in future trials.

Considerations

Generalization of these findings across RTT is limited by retrospective analysis and caregiver recall. Considering the inherent subjective limitations such as recall and/or confirmation bias, findings obtained by these techniques should be considered descriptive.^{108,109} The certainty of current

evidence remains variable. Nevertheless, methods to counteract these biases are evident across papers, including intra- and interrater reliability checks, as well as supplementation with objective methods (e.g. acoustic analysis). The trend towards objective speech-language analysis in RTT is promising and may offer greater reliability when capturing communicative acts, especially for therapeutics targeting the underlying cause of RTT with the greatest disease-modifying potential. Prominent techniques include eye tracking, acoustic analysis, and/or neuroimaging in conjunction with clinical expertise; the applicability of such techniques has been demonstrated in other conditions.^{110–112}

The scarcity of longitudinal data in this population is also evident. Although separate papers have characterized speech-language ability pre- and post-regression, few have tracked development across time. A continuous profile is necessary for understanding the impact of each clinical stage on communication, and distinguishing transient regression effects from stable trajectories. Future research should involve prospective longitudinal analysis, namely during the post-regression phase, and into adulthood with more advanced symptomatology.

One should also consider the predominance of studies involving classic RTT, relative to atypical forms (e.g. PSV-RTT). Typical phenotypes may have been overrepresented, concealing the broader spectrum of ability seen in atypical forms. Expanded database searches conducted during peer review were used to improve coverage of communication literature, and reduce the likelihood of overlooking relevant studies, including those which involved atypical RTT presentations.

Finally, it is necessary to consider access-related limitations when assessing communication in RTT. Expressive abilities are often more difficult to reliably measure than receptive abilities, given the severe motor and communication impairments characteristic of this population. Standardized assessments may not be fully accessible or sensitive to these limitations; for instance, participants may have limited control of alternative communication methods (e.g. hand-controlled devices), artificially lowering scores. As such, low performance may not reflect linguistic impairment in isolation, but rather the practical constraints of demonstrating one's knowledge. Adaptive methods (e.g. eye-tracking paradigms) may help refine descriptions of receptive and expressive competence.

CONCLUSION

This review consolidates current evidence on communication in Rett syndrome. A heterogeneous yet consistently atypical profile is observed across speech, language, and social ability. The communication profile is shaped by genetic variation, clinical stage, and age, with expressive language most severely impacted. Current methodologies are limited by their subjective nature, an inability to adequately assess non-verbal communication, and a lack of sensitivity to communication nuances in RTT. Greater objectivity is required to track change accurately across

time. Tools of automatic classification (AI) and/or acoustic analysis show promise as scalable, objective biomarkers; meaningful analysis may be possible through vocalizations alone, given the rarity of verbal language in RTT. Future research must prioritize longitudinal design with a focus on RTT-appropriate measures, to capture the full spectrum of communicative potential.

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CONFLICT OF INTEREST STATEMENT

APV is an employee of Redenlab Ltd, a speech neuroscience company. DNL is a consultant to Neurogene, Taysha Gene Therapies, and Acadia Pharmaceuticals. All other authors have stated that they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Search strings.

Appendix S2: JBI quality appraisals.

Appendix S3: All included studies.

Appendix S4: Full summary of communication-related measures and techniques.

Figure S1: PRISMA flow diagram for the primary search in this systematic review.

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