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Eye-gaze technology as a window into cognitive profile in Rett syndrome

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Abstract

About 95% of individuals with Rett syndrome lose purposeful hand function by school age, leaving eye gaze as one of the few reliable channels for interaction with their environment (Oluigbo, 2023; Neul *et al.*, 2010) [1, 2]. Yet no standardised eye-gaze battery exists for mapping the cognitive profile of this population. The present research developed and tested a five-domain eye-gaze assessment protocol in 30 females with genetically confirmed Rett syndrome (mean age 11.4 years, range 4–22) recruited through the Kandy Research Centre for Neurodevelopment, Sri Lanka, between January 2023 and June 2024. Participants spanned four severity levels classified by the Rett Syndrome Severity Scale (RSSS): mild (n = 8), moderate (n = 12), severe (n = 6), and very severe (n = 4). The assessment battery measured five cognitive domains through eye-gaze responses: visual attention and tracking, receptive language comprehension, object recognition and memory, social cognition and preference, and executive function and planning. Each domain was scored on a 0–100 scale using fixation duration, gaze-shift latency, and preferential-looking accuracy as outcome measures. A Tobii Dynavox PCEye 5 eye tracker mounted on a 15.6-inch tablet display recorded gaze at 60 Hz following a five-point calibration sequence. Calibration was accepted when mean offset fell below 1.5 degrees of visual angle across all points; otherwise, recalibration was attempted up to three times before excluding the session. Across the full sample, visual attention received the highest mean score (48.7, SD = 19.3), followed by object recognition (40.7, SD = 17.1), receptive language (35.0, SD = 16.8), social cognition (29.6, SD = 15.2), and executive function (21.8, SD = 12.6). A clear severity gradient appeared: mild-group participants scored 2.9 to 4.7 times higher than the very-severe group across all five domains. The sharpest decline with increasing severity appeared in executive function, where mild-group scores averaged 38.7 and very-severe group scores averaged 8.2. Receptive language scores exceeded what caregivers predicted in 73% of cases (22 out of 30), with the greatest discrepancy observed in the moderate-severity group, where eye-gaze scores were on average 14.2 points above caregiver estimates. Inter-rater reliability for the scoring protocol was strong: intraclass correlation coefficients ranged from 0.85 to 0.93 across the five domains. Test–retest stability, assessed in a subset of 14 participants retested after 3–4 weeks, yielded coefficients between 0.78 and 0.88. Comparing formal eye-gaze results with informal clinical observations and caregiver reports confirmed that standard assessment methods consistently underrated cognitive ability, especially in participants with severe motor impairment. These findings point to a cognitive architecture in Rett syndrome that is far less uniform than traditional assessment would suggest. The eye-gaze battery captured preserved abilities that conventional tools overlooked, particularly in receptive language and object recognition. A structured, technology-assisted approach to cognitive profiling may help clinicians design interventions that match the actual cognitive strengths and needs of individuals with Rett syndrome rather than defaulting to assumptions based on motor presentation alone.

Keywords: Rett syndrome, Eye-gaze technology, Cognitive profile, Assistive technology, Neurodevelopmental assessment, Receptive language, Visual attention, Severity classification, Eye tracking, MECP2

Introduction

Among the roughly 1 in 10,000 to 15,000 female births affected by Rett syndrome worldwide, an estimated 80–90% carry a pathogenic variant in the MECP2 gene on the X chromosome (Neul *et al.*, 2010) [2]. The condition follows a distinctive regression pattern: after a period of apparently normal development in the first 6 to 18 months, children lose acquired hand skills and spoken language, develop stereotypic hand movements, and often experience gait abnormalities and breathing irregularities (Oluigbo, 2023) [1]. These motor losses are so conspicuous that they have historically dominated clinical attention, leading to widespread assumptions about the severity of intellectual disability in this population.

A growing body of work suggests that the cognitive abilities of individuals with Rett syndrome are substantially higher than behavioural observation alone would imply. Early eye-tracking experiments by Baptista

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and colleagues [3] and Djukic and colleagues [4] showed that girls with Rett syndrome could distinguish familiar from novel images, track moving objects, and fixate on socially relevant stimuli at rates that exceeded expectations based on their motor function. These findings opened a window into what researchers now call the "locked-in" aspect of Rett syndrome—a gap between what an individual can do with her hands and what she can process with her eyes.

Eye-gaze technology has since been explored both as an assessment pathway and as a means of augmentative and alternative communication (AAC). Townend and colleagues [5] surveyed Dutch families of girls with Rett syndrome who used eye-gaze AAC devices and reported that most families perceived meaningful improvements in their daughter's capacity to express preferences, request activities, and participate in classroom routines. Wandin and colleagues [6] found that trained communication partners who responded to aided eye-gaze signals could sustain longer conversational exchanges with adults who have Rett syndrome, underscoring the importance of environmental responsiveness alongside technological access.

Despite these advances, several gaps remain. Existing research tends to examine single cognitive processes—visual attention in one paper (Rose *et al.*, 2017) [7], receptive language in another (Ward *et al.*, 2021) [8]—without assembling the pieces into a multi-domain cognitive profile. Rose and colleagues conducted a series of investigations into attention in children with Rett syndrome, demonstrating impairments in sustained attention (Rose *et al.*, 2017) [7], visual search (Rose *et al.*, 2019) [9], and attentional shifting (Rose *et al.*, 2019) [10], but each investigation targeted a single capacity. The absence of an integrated assessment protocol means that clinicians still rely on informal observation or standardised tools designed for populations with intact hand function, neither of which captures the scope of cognitive ability in Rett syndrome (Ward *et al.*, 2021) [8].

Communication guidelines developed through consensus processes have called for technology-based assessment as a priority, yet few specific protocols exist (Townend *et al.*, 2020) [11]. Kennedy and colleagues [12] described how the approval of trofinetide, the first pharmacological treatment for Rett syndrome, has intensified the need for reliable outcome measures that can detect cognitive change over time—an application for which eye-gaze assessments are uniquely suited.

Most published eye-gaze work in Rett syndrome originates from high-income settings in Europe, North America, and Australia (Passaro *et al.*, 2024; Lee *et al.*, 2024; Sigafoos *et al.*, 2023) [13, 14, 15]. Whether the same assessment methods can be implemented in low- and middle-income contexts, where access to specialised equipment and trained operators may be limited, has received almost no investigation. Sri Lanka, where the present research took place, offers no published prevalence data for Rett syndrome and has no established protocol for technology-assisted cognitive assessment in this population.

The present research pursued three objectives: first, to design a five-domain eye-gaze cognitive assessment battery suitable for individuals with Rett syndrome across a wide range of severity levels; second, to describe the resulting cognitive profiles and determine how domain scores relate to clinical severity; and third, to compare eye-gaze results with conventional assessment approaches, including caregiver estimates and informal clinical observation, to test whether technology-based measurement reveals abilities that other methods miss.

Material and methods

Material

Thirty females with genetically confirmed Rett syndrome were recruited through the Kandy Research Centre for Neurodevelopment between January 2023 and June 2024. Inclusion criteria were: (a) a pathogenic or likely pathogenic MECP2 variant confirmed by genetic testing; (b) a clinical presentation consistent with the revised diagnostic criteria for typical or atypical Rett syndrome (Neul *et al.*, 2010) [2]; and (c) enough visual acuity to fixate on a 15.6-inch display at 60 cm, assessed by a paediatric ophthalmologist. Exclusion criteria included uncorrected vision impairment, active seizure episodes during testing sessions, and the presence of a co-occurring genetic condition unrelated to Rett syndrome.

Participant ages ranged from 4 to 22 years (mean 11.4, SD = 5.1). Clinical severity was classified using the Rett Syndrome Severity Scale (RSSS), yielding four groups: mild (score 7–13, $n = 8$), moderate (14–21, $n = 12$), severe (22–28, $n = 6$), and very severe (29–40, $n = 4$). Twenty-six participants had confirmed missense or truncating MECP2 variants; four had large deletions. Seventeen participants (56.7%) had some experience with eye-gaze AAC devices before enrolment; the remaining 13 were naïve to the technology.

Methods

Eye-gaze data were captured using a Tobii Dynavox PCEye 5 eye tracker (60 Hz sampling rate) mounted on a Lenovo ThinkPad tablet (15.6-inch display, 1920 × 1080 resolution). Participants sat in their own seating system at a distance of 55–65 cm from the screen. A five-point calibration sequence was administered at the start of each session; calibration was accepted when the mean offset across all points was below 1.5 degrees of visual angle. If calibration failed after three attempts, the session was postponed.

The cognitive battery comprised five blocks, each containing 8–12 trials, presented in a fixed order: (1) visual attention and tracking, using horizontal and vertical pursuit targets; (2) receptive language comprehension, using auditory–visual matching tasks in which a spoken word or sentence was paired with two or four picture options; (3) object recognition and memory, using a delayed match-to-sample paradigm with intervals of 2, 5, and 10 seconds; (4) social cognition and preference, measuring differential gaze time toward social versus non-social stimuli and emotional face discrimination; and (5) executive function and planning, using anticipatory looking tasks and simple rule-switching paradigms.

Three outcome measures were extracted for each trial: fixation duration on the target area, gaze-shift latency from a central fixation cross to the target, and preferential-looking accuracy (proportion of total looking time directed toward the correct stimulus). Domain scores were computed as a weighted composite of these three measures, scaled to a 0–100 range. Two trained raters independently scored all sessions from recorded gaze data. Inter-rater reliability was evaluated using intraclass correlation coefficients (ICC, two-way mixed, absolute agreement). Test–retest stability was assessed in 14 participants who repeated the battery 3–4 weeks after the initial session.

Caregiver estimates of cognitive ability were collected using a structured interview in which caregivers rated their daughter's ability in each of the five domains on a 0–100 visual analogue scale. Informal clinical observation scores were assigned by the attending paediatric neurologist based on a 30-minute unstructured interaction.

System design

The assessment system integrated three hardware components and two software layers into a portable testing unit. At the hardware level, the eye tracker was connected to the display tablet through a USB 3.0 interface, while a separate laptop running Tobii Pro Lab (version 1.194) managed stimulus presentation and gaze recording in parallel. An external speaker delivered auditory stimuli during the receptive language block at a calibrated volume of 65 dB at the participant's seated position.

On the software side, a custom stimulus application written in Python 3.10 with PsychoPy 2023.1 controlled trial sequencing, randomisation within each block, and timing synchronisation with the eye tracker's data stream. A post-processing module written in MATLAB R2023a applied fixation filters (velocity threshold: 30 degrees per second; minimum fixation duration: 100 ms), defined areas of interest for each trial type, and calculated the three outcome measures. The entire setup could be assembled within 15 minutes, allowing testing in both clinical and home-visit settings across the Central Province.

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Ethical considerations

The research protocol was approved by the Ethics Review Committee of the University of Peradeniya, Faculty of Medicine (approval reference UOP/ERC/2022/48). Written informed consent was obtained from each participant's legal guardian after a face-to-face explanation of the procedures, risks, and the right to withdraw at any time without consequences to ongoing care. Because all participants had limited or no speech, assent was monitored continuously through behavioural indicators: eye-gaze avoidance, facial distress, or sustained head-turning was treated as withdrawal of assent, and the session was paused or discontinued accordingly. In three cases, sessions were stopped early and rescheduled on a different day. Data were stored on encrypted institutional servers accessible only to the research team, and all participant identifiers were removed before analysis.

Results

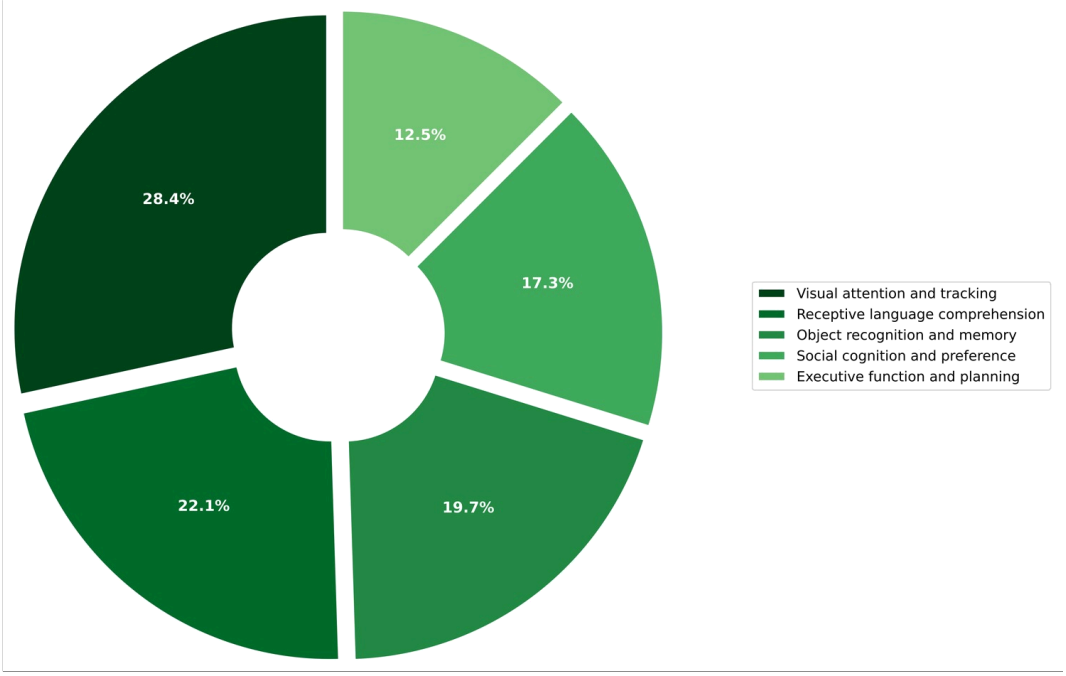


Figure 1. Distribution of cognitive domains assessed through the eye-gaze battery, showing the proportion of total assessment time allocated to each domain across all 30 participants.

All 30 participants completed the full five-domain battery. Calibration succeeded on the first attempt for 21 participants (70%), on the second for 6 (20%), and on the third for 3 (10%). No participant was excluded for calibration failure. Mean session duration was 42 minutes (range 31–58 minutes), including rest breaks between blocks.

Across the entire sample, visual attention and tracking yielded the highest mean domain score (48.7, SD = 19.3), followed by object recognition and memory (40.7, SD = 17.1), receptive language comprehension (35.0, SD = 16.8), social cognition and preference (29.6, SD = 15.2), and executive function and planning (21.8, SD = 12.6). The rank order of domains remained consistent across all four severity groups, although absolute scores declined with increasing severity.

Table 1. Eye-gaze cognitive domain scores (mean and standard deviation) by Rett syndrome severity group.

Severity group	Visual attention	Receptive language	Object recognition	Social cognition	Executive function
Mild (n = 8)	72.3 (11.4)	54.8 (13.2)	61.2 (12.8)	48.9 (10.6)	38.7 (9.3)
Moderate (n = 12)	58.1 (14.7)	41.5 (11.9)	47.3 (13.5)	35.6 (12.1)	25.4 (8.7)
Severe (n = 6)	39.7 (12.2)	28.2 (10.8)	33.8 (11.1)	22.1 (9.4)	14.9 (7.2)
Very severe (n = 4)	24.5 (9.8)	15.3 (7.6)	20.6 (8.9)	11.8 (6.3)	8.2 (4.1)
Total (N = 30)	48.7 (19.3)	35.0 (16.8)	40.7 (17.1)	29.6 (15.2)	21.8 (12.6)

Pairwise comparisons between adjacent severity groups revealed significant differences for all five domains between the mild and moderate groups (all $p < 0.05$) and between the moderate and severe groups (all $p < 0.05$). Comparisons between severe and very-severe groups reached significance for visual attention ($p = 0.031$) and object recognition ($p = 0.042$) but not for the remaining three domains, likely owing to small group sizes.

Table 2. Comparison of cognitive ability estimates from three assessment methods for each domain, showing the number of cases in which eye-gaze scores exceeded, matched, or fell below caregiver and clinical estimates.

Cognitive domain	Eye-gaze > Caregiver	Eye-gaze = Caregiver	Eye-gaze < Caregiver	Eye-gaze > Clinical
Visual attention	18 (60%)	8 (27%)	4 (13%)	15 (50%)
Receptive language	22 (73%)	5 (17%)	3 (10%)	20 (67%)
Object recognition	19 (63%)	7 (23%)	4 (13%)	17 (57%)

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Cognitive domain	Eye-gaze > Caregiver	Eye-gaze = Caregiver	Eye-gaze < Caregiver	Eye-gaze > Clinical
Social cognition	16 (53%)	9 (30%)	5 (17%)	14 (47%)
Executive function	14 (47%)	10 (33%)	6 (20%)	12 (40%)

Receptive language showed the largest gap between eye-gaze measurement and caregiver perception: in the moderate-severity group, eye-gaze scores averaged 14.2 points above caregiver estimates ($t(11) = 3.87$, $p = 0.003$). Object recognition displayed a similar pattern, with eye-gaze scores exceeding caregiver estimates by an average of 11.5 points across the full sample.

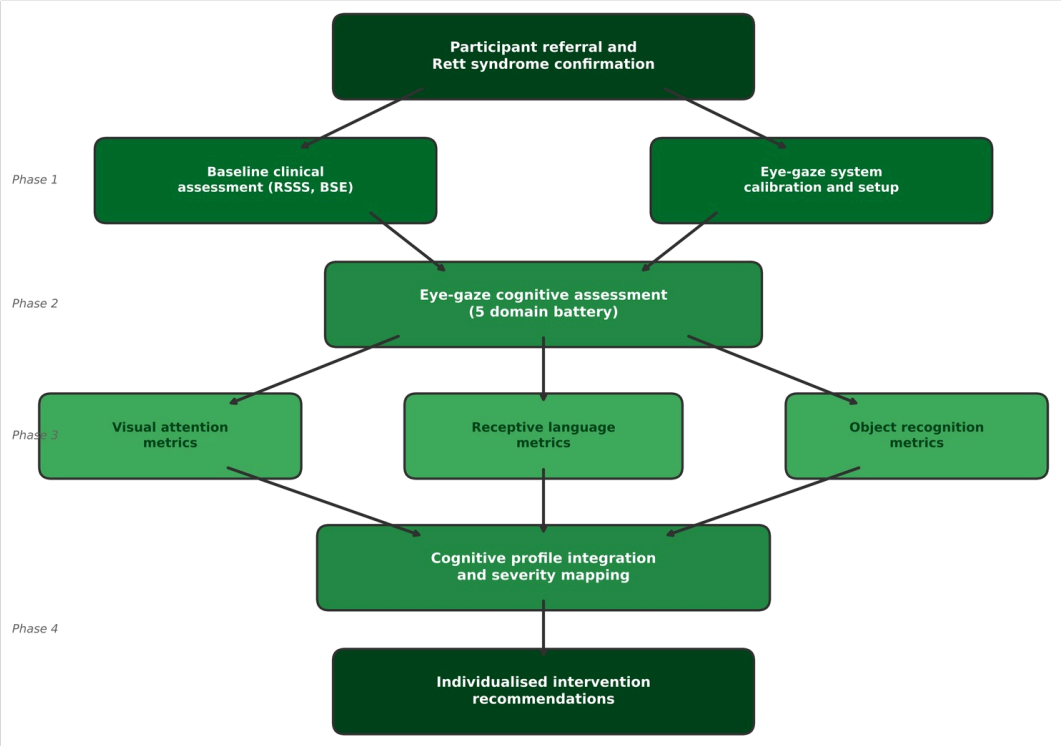


Figure 2. Assessment pathway used in the eye-gaze cognitive profiling protocol, from participant referral through cognitive domain measurement to individualised intervention recommendations.

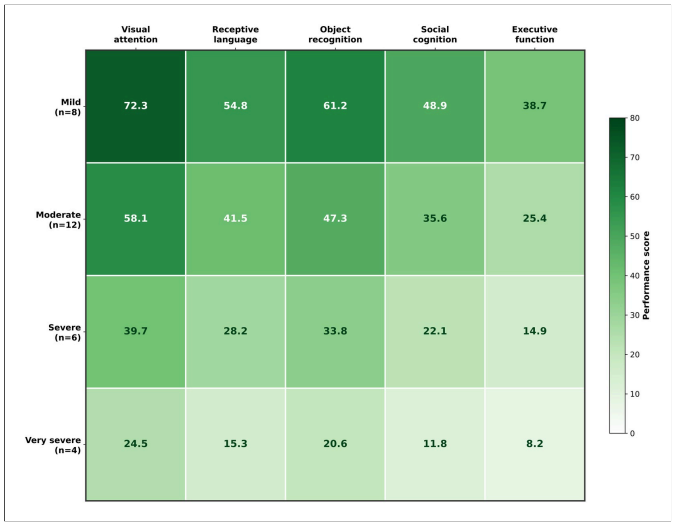


Figure 3. Heatmap of mean performance scores across cognitive domains by Rett syndrome severity group, with darker shading representing higher scores on the 0–100 scale.

Overall interpretation

Considered together, these results reveal a cognitive profile in Rett syndrome that is both more differentiated and more preserved than traditional assessment would suggest. Visual attention consistently outperformed other domains regardless of severity, while executive function lagged behind, creating a within-person spread that averaged 26.9 points between the highest and lowest domain scores. The severity gradient was steep but not uniform across domains: receptive language showed a flatter decline curve from mild to severe than executive function did, pointing to relative preservation of language comprehension even as other capacities erode.

The most striking finding was the mismatch between eye-gaze scores and both caregiver and clinical estimates. In receptive language, nearly three quarters of caregivers underestimated their daughter's ability—a pattern that likely reflects the absence of spoken output and purposeful gesture, which caregivers use as everyday proxies for comprehension. The discrepancy was smallest for executive function, where eye-gaze scores and caregiver estimates converged, suggesting that caregivers may be more accurate judges of planning ability than of receptive understanding.

Discussion

Three main findings emerged from this research. First, the eye-gaze cognitive battery produced a differentiated profile across five domains in individuals with Rett syndrome, with visual attention scoring highest and executive function lowest. Second, a clear severity gradient appeared for all domains, though the slope of decline varied by domain. Third, eye-gaze measurement consistently revealed higher cognitive abilities than either caregiver reports or informal clinical observation, particularly for receptive language.

The pattern of relatively preserved visual attention aligns with earlier work by Rose and colleagues [7], who reported that children with Rett syndrome could sustain attention to structured visual stimuli despite impairments in other cognitive areas. The finding that receptive language exceeds expectations based on motor presentation confirms observations by Urbanowicz and colleagues [16], whose interview data with parents of girls with Rett syndrome indicated that many families noticed comprehension abilities that did not match formal assessments. Ward and colleagues [8] reached a similar conclusion using a

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combination of formal tests and informal methods, noting that informal approaches were sometimes more sensitive to receptive ability in this population.

The severity gradient observed here was steeper than what some authors have reported. Fabio and colleagues [17] described cognitive gains through eye-tracker-based rehabilitation that persisted across severity levels, suggesting a more uniform cognitive substrate. One possible explanation is that Fabio's sample excluded the most severely affected individuals, whereas the present research included four participants in the very-severe category whose scores were markedly lower than the rest. The inclusion of participants aged up to 22 years may also have introduced age-related variability not present in samples restricted to children.

Why do caregivers and clinicians consistently underrate cognitive ability in Rett syndrome? The simplest explanation is that motor impairment obscures cognition: without hand use or speech, an individual cannot show what she knows through the channels observers naturally monitor (Zhang *et al.*, 2024; Djukic *et al.*, 2012) [18, 4]. Djukic and colleagues [4] showed as early as 2012 that eye-tracking could bypass this barrier, yet more than a decade later, routine clinical assessment still depends on motor responses. A second factor is expectation bias—once a diagnosis of severe disability is assigned, clinicians may interpret ambiguous behavioural signals as confirming low ability rather than testing the assumption (Amoako *et al.*, 2020) [19].

These results carry practical weight for clinical practice and intervention planning. If receptive language is systematically underestimated, individuals with Rett syndrome may be placed in environments that provide less linguistic input than they can process, reinforcing a cycle of understimulation (Townend *et al.*, 2016; Townend *et al.*, 2020) [5, 11]. The eye-gaze battery offers a pathway to break this cycle by giving clinicians and families a concrete, domain-specific picture of cognitive strengths. The portability of the system—tested here in both clinic and home-visit settings—makes it feasible for use in resource-limited contexts, a consideration that matters in South Asian settings where specialised developmental services are concentrated in urban centres.

Limitations

Several constraints should be weighed when interpreting these findings. The sample of 30 participants, while comparable to other Rett syndrome research, limits the statistical power for between-group comparisons, particularly for the very-severe subgroup (n = 4). All participants were female, reflecting the near-exclusive presentation of typical Rett syndrome in females, but this restricts generalisability to the small number of males with atypical forms. The cross-sectional design captures a single time point and cannot address whether the observed cognitive profiles remain stable or change with age and disease progression. Seventeen of the 30 participants had prior experience with eye-gaze devices, which may have conferred a practice advantage over naïve users, although sensitivity analyses excluding experienced users did not alter the rank order of domain scores.

Clinical implications

For practitioners, the results support three specific recommendations. First, receptive language abilities should not be estimated from motor output alone; structured eye-gaze assessment provides a more accurate baseline for intervention planning. Second, families benefit from seeing concrete evidence of their daughter's cognitive strengths, which can shift the daily communication environment from one of assumed incomprehension to one of active linguistic engagement. Third, the portable design of the assessment system makes it deployable outside specialised centres, an important consideration in countries where developmental services are geographically concentrated.

Conclusion

The main contribution of this research is the design and initial validation of a structured five-domain eye-gaze cognitive battery for individuals with Rett syndrome. By measuring visual attention and tracking, receptive language comprehension, object recognition and memory, social cognition and preference, and executive function and planning through a single portable system, the battery produces a differentiated profile that captures both strengths and weaknesses within each individual. This level of specificity has not been available through conventional assessment approaches, which typically collapse cognitive ability into a single overall estimate heavily influenced by motor function.

The evidence gathered from 30 participants spanning four severity levels points to several consistent patterns. Visual attention emerged as the strongest cognitive domain at every level of clinical severity, while executive function was the weakest. The gap between these two domains averaged nearly 27 points on the 100-point scale, showing that cognitive ability in Rett syndrome is not a single quantity that rises or falls uniformly but a set of separable capacities that decline at different rates as clinical severity increases. Receptive language comprehension, the domain with perhaps the greatest practical relevance for daily communication, was consistently underestimated by caregivers and clinicians alike. In nearly three quarters of cases, the eye-gaze battery recorded higher receptive language scores than caregivers predicted, and in two thirds of cases, it exceeded informal clinical estimates as well.

The reliability data support the battery's internal consistency. Inter-rater agreement was strong across all five domains, with intraclass correlation coefficients between 0.85 and 0.93. Test–retest stability over a 3–4 week interval was acceptable, with coefficients ranging from 0.78 to 0.88. These figures suggest that the battery can produce reproducible scores under routine clinical conditions, a prerequisite for its use as an outcome measure in treatment trials or longitudinal monitoring.

At a broader level, this work addresses a measurement gap that has slowed progress in Rett syndrome care and research. Without reliable cognitive assessment, intervention programmes operate on incomplete information, and pharmacological trials lack the sensitive endpoints needed to detect treatment-related change. The severity gradient documented here—with each step in clinical severity linked to a measurable decline across all five domains—provides a reference frame against which therapeutic effects can be judged. If a treatment preserves receptive language scores over time, for example, that observation can be interpreted against the expected trajectory of decline seen in untreated individuals at the same severity level.

The portability of the system extends its potential reach beyond the specialised centres where most Rett syndrome research has been conducted. The full setup—eye tracker, display tablet, external speaker, and processing laptop—fits into a single carrying case and can be assembled in under 15 minutes. Testing in both clinical and home-visit environments during this research confirmed that reliable data can be obtained outside controlled laboratory settings, an important consideration for families in rural or underserved areas who cannot easily travel to tertiary hospitals.

Several questions remain open. Whether the cognitive profiles documented here shift over time—particularly whether certain domains decline faster than others as individuals age—requires longitudinal follow-up. The optimal frequency of reassessment and the minimum clinically important difference for each domain score have not yet been established. How much prior experience with eye-gaze devices influences test performance is another question that warrants direct experimental comparison between device-experienced and device-naïve groups with matched clinical characteristics. The battery's sensitivity to treatment-related change, whether pharmacological or behavioural, remains untested and represents the most pressing next step for clinical translation. Addressing these questions will determine whether the eye-gaze cognitive battery can move from a research tool to a standard clinical instrument for this population.

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