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Application of Eye-Tracker to Individuals with Rett Syndrome: A Systematic Review

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Abstract

Eye-tracking technology is an emerging tool to monitor eye gaze non-invasively. This technique has been adopted widely to investigate eye gaze during visual stimuli and tasks in health and disease. We reviewed studies that aimed to determine the application of an eye-tracker for individuals with Rett syndrome. A systematic search identified eight studies that were summarized in terms of main purpose, subject, study design, eye-tracking technology, main parameter, and primary finding of interest. The main purposes of the reviewed studies were to evaluate cognitive function, judge habilitation intervention outcomes, and demonstrate that both epilepsy features and electroencephalography characteristics are correlated with the ability to recognize and match pairs and categorize semantically with respect to animals and behavioural features. The eight studies included 193 individuals with Rett syndrome, ranging from 1.5 to 31 years of age. Four of the eight studies included typically developing female participants as a control group to compare eye gaze features. The reviewed studies could enable family members and care staff to know intentionality, recognize facial expressions and concepts of colour, shape, size, and spatial position, the strict correlation between neurophysiological features and neuropsychological impairment, preference for socially weighted stimuli and for novel and salient stimuli, attention and recognition memory, and habilitation outcomes. We suggest that the findings obtained by this technique should be utilized to evaluate and examine habilitation plans and means, judge intervention outcomes, and identify correlations between neurophysiological features and neuropsychological impairment and are of significant benefit to know the hidden and potential abilities of individuals with Rett syndrome.

Keywords: Fixation; Eye gaze; Eye tracking; RTT; Profound intellectual multiple disabilities; Severe motor and intellectual disabilities

Introduction

Rett syndrome (RTT; OMIM #312750) was described originally in the German literature in 1966 by Andreas Rett [1]. The current diagnostic criteria for typical or classic RTT are: 1) a period of regression followed by recovery or stabilization; and 2) all main criteria and all exclusion criteria are required [2]. The main criteria include: 1) partial or complete loss of acquired purposeful hand skills; 2) partial or complete loss of acquired spoken language; 3) gait abnormalities: impaired (dyspraxic) or absence of ability; and 4) stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms. Included in the exclusion criteria are: 1) brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems; and 2) grossly abnormal psychomotor development in the first 6 months of life. Atypical RTT is diagnosed when there are: 1) a period of regression followed by recovery or stabilization; 2) at least 2 of the 4 main criteria; and 3) at least 5 of the 11 supportive criteria [2].

The estimated number of define Rett syndrome patients in Japan was 1,011 (95% confidential interval, 778–1,244), and the estimated prevalence was 9 per 100,000 [3]. Generally, after a period of normal development, a healthy-looking baby girl falls into developmental stagnation, which is followed by rapid deterioration, loss of acquired speech, and the replacement of the purposeful use of hands with incessant stereotypies, a characteristic of the syndrome [4]. Early developmental skills are acquired by many, but clear differences from normality emerge, particularly in skills expected after the age of 6 months [5].

A range of behaviors of individuals with RTT was reportedly used for communication, including eye positioning/eye gaze, body movements, leading, clapping, reaching, pushing away items, and tantrums/screaming [6]. Eye gaze has been considered to be the most important way in which individuals with RTT express their will, communicate, learn about the world, and interact with their surroundings [7-22]. Objective eye movements allow families and care staff to achieve more detailed spatial and temporal resolution of oculomotor behavior, make more precise quantitative determinations of eye-movement characteristics, such as the response gain, and generate permanent records [23]. An eye-tracking system is a set of methods and techniques that allow the detection of both eye movements and fixations performed during a visual interaction in a given context and facilitate communicative functions of gaze favoring a successful outcome in many areas of rehabilitation [24].

Few reports have focused on a literature review about the application of eye-tracking technology to individuals with RTT. We hope that this systematic review can expand the range of the utility of the eye-tracker. Consequently, the purpose of this article was to review the literature with respect to studies in which an eye-tracker has been used on individuals with RTT.

Materials and Methods

Literature search criteria and data extraction

The following combinations of Keywords were used in a Medline literature search: “Rett syndrome” and “eye tracking,” “eye tracker,” “eye gaze tracking,” “eye movement,” “gaze,” or “fixation.” The “Related citations” function was utilized to broaden the search, and all titles and abstracts were scanned and reviewed. The keywords: “eye tracking,” “eye tracker,” and “eye gaze tracking” were used in a previous review study [24]. The last date for this literature search was May 18, 2015. The following data were extracted independently from each study by the two reviewing authors: first author, year of publication, main purpose, subject, study design, eye-tracking technology, main parameter, and primary finding of interest.

Inclusion and exclusion criteria

In order to be included in this review, studies had to use an eye-tracking instrument to investigate eye gaze to stimuli/tasks on a monitor screen and include at least one person with a diagnosis of RTT. Studies were limited to those in the English language. Review articles and comment papers were also excluded.

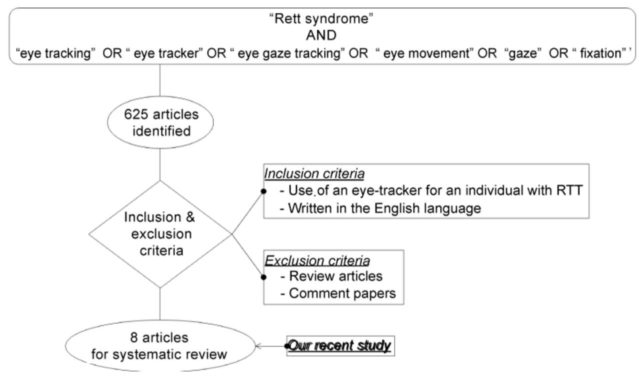

Figure 1: Systematic review search strategy. The systematic search strategy, highlighting the number of articles acquired in the original search, the justification for rejection of certain articles, and the total number of articles included for systematic review, data extraction, and analysis.

Study identification

In the initial literature search, 625 publications were identified. Of these, 618 articles were excluded following title and abstract review. Our recent study was also added to this review. This left a total of 8 studies that were investigated in detail. The search strategy is summarized in Figure 1.

Results

Table 1 provides a summary of the eight included studies. The table indicates a summary of each first author, year of publication, main purpose, subjects, study design, eye-tracking technology, main parameter, and primary finding of interest.

References	Main purpose	Subject	Study design	Eye-tracking technology	Main parameter	Primary finding of interest
[25]	To verify whether RTT girls are able to respond to simple verbal instructions, recognize and match objects, and categorize similar objects.	RTT: N=7	Three tasks were designed: (1) response to verbal instruction (look at the dog, look at the picture of your father, etc.); (2) recognition and matching pairs (look at the one that is the same); and (3) semantic categorization (look at the one that is similar). Twelve different pictures, divided into three groups (fruit [papaya, apple, orange, and banana]; animals [dog, cat, bird, and fish]; and people [father, mother, the child herself, and some unknown people]) were used. Each item was shown for 5s.	Eyegaze device and Passive Gaze Tracing software (LC Technologies, Sao Paulo, Brazil) were used. The girls were sitting on their parent’s lap, approximately 50 cm away from the monitor (15 inches).	Length of fixation	The comparison of fixation time on the alternatives revealed a higher percentage (62.4%) of correct alternatives (X2=76.31; P=0.000). Of the seven children assessed, only one did not present predominance of fixation on the correct alternatives in any one of the tasks. One did well in all tasks. Six responded correctly to all verbal instructions.
[26]	To evaluate recognition of the concepts of color (red, yellow, and blue), shape (circle, square, and triangle),	RTT: N=10	The images were presented on a board that exhibited, inside circles, the three colors and a different color (green). The board contained the three shapes and a different one (cross). On the board relative to size and position, there was a larger and a smaller circle and one circle above and below. The evaluation included 10 verbal	Tobii 1750 device and ClearView software (Tobii Technology AB, Danderyd, Sweden) were used.	Length of fixation	The time of eye fixation on the required and not required concepts did not differ significantly. Children did not indicate recognition of the required concepts with their eyes when assessed with an eye-tracking system.

	size (big and small), and spatial position (over and under).		commands given to the children in the following order: "Look at: yellow, red, blue, triangle, square, circle, big, small, over, and under." A permanence of 3 s for the mediator boards and 4 s for the boards that contained the solicited concepts was used.	Monitor size was 17 inches.		
[29]	To delineate if and how neurological and neurophysiological impairment reflects behavioral and neuropsychological functions.	RTT: N=18	Three tasks were designed: (1) response to verbal instruction (look at the dog, etc.); (2) recognition and matching of pairs (look at the one that is the same); and (3) semantic categorization (look at the one that is similar). The images used were of objects familiar to the children, according to their parents. Nine different pictures were divided into three groups: fruit—apple, orange, and banana; animals—dog, cat, and horse; and emotions—happy, sad, and angry. Each item was presented for 5 s.	Eyegaze device and Passive Gaze Tracing software (LC Technologies, Sao Paulo, Brazil) were used. The girls sat on their parent's lap, approximately 20 cm away from the monitor (15 inches).	Length of fixation	Age at epilepsy onset and seizure frequency were strictly correlated with neuropsychological outcome, as were EEG stage and distribution of paroxysmal abnormalities.
[30]	To examine the pattern of visual fixation and social preferences in girls with RTT.	RTT: N=49 TD: N=33	Three pictures were presented: (1) face; (2) people vs. object; and (3) realistic complex visual scene. Each picture was presented for 5 s. Verbal instructions were limited to the prompt "Look at the TV," which was used at the beginning of the session.	Tobii T120 device and Tobii Studio software (Enterprise editions) (Tobii Technology AB, Danderyd, Sweden) were used. The participants were seated in their parents' lap. They were seated 3050 cm away from the monitor.	Length of fixation Number of fixations	They looked at people and into people's eyes.
[31]	To determine (1) the basic features of nonverbal cognitive processes in girls with RTT, such as the characteristics of their visual fixation pattern (meaningful vs. random) and visual attention (in response to novelty) and (2) the feasibility of eye-tracking as a method for cognitive assessment in girls with RTT.	RTT: N=44 TD: N=33	Two pictures were presented: (1) discrimination of the salience of visual stimuli and (2) attention to novelty. Each picture was presented for 5 s. Verbal instructions were limited to the prompt "Look at the TV," which was used at the beginning of the session.	Tobii T120 device and Tobii Studio software (Enterprise editions) (Tobii Technology AB, Danderyd, Sweden) were used. The participants were seated in their parents' lap. They were seated 3050 cm away from the monitor.	Length of fixation Number of fixations	Of the 44 participants, 35 were calibrated and exhibited meaningful patterns of visual fixation. They looked longer at salient stimuli (cartoon, 2.8 ± 2 s S.D., vs. shape, 0.9 ± 1.2 s; P=0.02), regardless of their position on the screen. They recognized novel stimuli, decreasing the fixation time on the central image when another image appeared on the periphery of the slide (2.7 ± 1 s vs. 1.8 ± 1 s, P=0.002).
[32]	To seek to bypass the motoric and verbal disabilities	RTT: N=27 TD: N= 30	The VPC paradigm was used. There were nine problems: five using achromatic photos of faces and four using multicolored abstract patterns. For each problem, two identical stimuli were presented briefly	Tobii TX300 device and Tobii Studio software (Enterprise	Length of fixation Number of fixations	Although participants with RTT showed recognition of both faces and patterns, with novelty scores greater than chance (50%), their performance was significantly poorer than that of the typically developing

	associated with RTT and capitalize on their presumed visual strengths by assessing attention and recognition memory.		side-by-side for familiarization (10 s for faces, 5 s for patterns); then the familiar stimuli and a new one were paired in the test (10 s for both, with left–right positions reversed after the first 5 s, to control for side preferences). Verbal instructions, limited to "Look at the TV," were used at the beginning of the session.	edition) (Tobii Technology AB, Danderyd, Sweden) were used. All participants with RTT (and all TD<12 y) were seated on their parent's lap. They were seated approximately 45 cm from the monitor (23 inches).	Looking time Gaze dispersion	comparison group. Their attention to both was less mature and marked by a more narrowly focused gaze, with fewer and longer fixations. When inspecting faces, attention to the eyes was similar in both groups; however, participants with RTT tended to ignore the nose and mouth.
[33]	To examine the ability to recognize "facial expression."	RTT: N=37 TD: N=34	The VPC paradigm was used. The stimuli, 12 digitized color photographs, consisted of six different female models, each presenting two expressions: happy/sad, happy/fear, or sad/fear. On each problem, two identical faces, both presenting the same emotion, were initially presented side-by-side for 10 s (familiarization phase). Then, the previously viewed face was paired with a new one, in which the same model presented a different expression (test phase). The test lasted for 10 s (with a left-right reversal of novel and familiar targets after the first 5 s to control for side bias). Verbal instructions, limited to "Look at the TV," were used at the beginning of the session.	Tobii TX300 device and Tobii Studio software (Enterprise edition) (Tobii Technology AB, Danderyd, Sweden) were used. All participants with RTT (and all TD<12 y) were seated on their parent's lap. They were seated approximately 45 cm from the monitor (23 inches).	Length of fixation Number of fixations Looking time Gaze dispersion	Individuals with RTT had difficulty recognizing most emotional expressions, unlike the typically developing comparison group. Also, their scanpaths were atypical with less looking, fewer and/or longer fixations, and less time devoted to all facial features (48% vs. 72%), particularly the mouth. Significant correlations between looking to critical features and recognition underscored the importance of scanning.
[34]	To examine the effect of longitudinal habilitation intervention upon fixation duration in an individual with RTT.	RTT: N=1	Fixation duration in two tasks (tasks 1 and 2) was recorded at the start of intervention and at 1, 2, and 3 weeks later. In task 1, 2 colored squares (red and blue) were displayed simultaneously for 5 s, followed by a white background for 5 s. In task 2, a red and a blue square were presented simultaneously for 5 s, followed by a photograph of her care staff for 5 s, which was displayed on the same side of the screen as the red square. This cycle was repeated 10 times in both tasks. To develop the participant's ability to change fixation target, we used mainly verbal and nonverbal instructions with emotional communication from her care staff for 10 min, 5 days a week.	Tobii TX300 device and Tobii Studio software (Enterprise edition) (Tobii Technology AB, Danderyd, Sweden) were used. The participant sat in a seating system located approximately 65 cm away from the monitor (23 inches).	Length of fixation	Fixation duration to the experimental targets was significantly improved after intervention for 3 weeks compared with before intervention.
RTT: Rett syndrome; TD: Typical Development; VPC: Visual Paired-Comparison [20,36,37]						

Table 1: Overview of eye-tracking research studies.

Purpose

The main purposes of the reviewed studies for RTT using an eye-tracker were to evaluate cognitive function, judge the outcomes of habilitation intervention, and demonstrate a strict correlation between neurophysiological features and neuropsychological impairment. An eye-tracking system was used to verify whether girls with RTT use their gaze intentionally, by observing their performance in three cognitive tasks: (1) verbal instruction condition (look at picture X); (2) recognition and matching of pictures (look at the one that is the same); and (3) categorization of pictures (look at the one that is similar) [25], to assess their ability to indicate with their eyes the recognition of concepts of color (red, yellow, and blue), shape (circle, square, and triangle), size (big and small), and spatial position (over and under) [26], to verify if neurophysiological and epileptological characteristics could be correlated with cognitive measures, obtained using eye-tracker technology, and behavioral scores (Vineland Adaptive Behavior Scales [VABS], which are organized in four domains: communication; daily living; socialization; and motor skills [27] and Rett Assessment Rating Scale [RARS], which allows the evaluator to identify the level of severity of RTT [28]) [29], to examine nonverbal cognitive abilities and visual preferences [30], to examine nonverbal cognitive abilities and the basic features of visual processing (visual discrimination attention/memory) [31], to examine attention and recognition memory for faces and patterns [32], to examine recognition of emotional expressions [33], and to examine the effect of longitudinal habilitation intervention by care staff upon fixation duration in an individual with RTT [34].

Participants' Characteristics

Table 2 provides a summary of the characteristics of the participants in the included studies. The eight studies assessed a total of 193 females with RTT and 130 typical development (TD) females (age- and gender-matched). The participants with RTT ranged from 1.5 to 31 years of age. Mean age could not be calculated because two studies did not specify the precise age of each participant. Of the eight studies, six provided the characteristics of the individuals with RTT [25,26,29,32-34]. Four studies performed a comparison with TD female participants [30-33], and one study was a case report [34]. In many studies, the participants' information for age, genetics, and walking were described as personal characteristics. Clinical stage, seizure, VABS [27], Rett Syndrome Severity Scale [35], and age at regression were also reported.

References	N	Mean age	Each age	Genetics	Walking	Clinical stage	Seizure	VABS total score	RSSS total score	Age at regression	Speech	Hand use
[25]	RTT=7	Mean=6.6 y Range=4.1-9.6 y	+	+	+	+	-	-	-	-	+	+
[26]	RTT=10	Range=4 y 8 m-12 y 10 m	+	+	-	+	-	-	-	-	-	-
[29]	RTT=18	Mean=13.7 y Range=7-21 y	+	+	-	+	+	+	-	-	-	-
[30]	RTT=49	Mean=9 y, SD=6 y Range=1.5-25 y	-	-	-	-	-	-	-	-	-	-
	TD=33	Mean=12.2 y, SD=6.5 y										
[31]	RTT = 44	Mean = 10 y, SD = 6 y	-	-	-	-	-	-	-	-	-	-
	TD=33	Mean=12.2 y, SD=6.5 y										
[32]	RTT=27	Mean=10 y 6 m, SD=6 y 8 m Range=2-22 y	+	+	+	-	+	+	+	+	-	-
	TD=30	Mean=10 y 6 m, SD=5 y 6 m Range=2-22 y										
[33]	RTT=37	Mean=10.0 y, SD=10.0 y Range=2-31 y	+	+	+	-	+	+	+	+	-	-
	TD=34	Mean=12.0 y, SD=6.5 Range=2-30 y										

[34]	RTT=1	23 y	+	-	+	-	-	-	-	-	+	+

RTT: Rett syndrome; TD: Typical Development; SD: Standard Deviation; VABS: Vineland Adaptive Behavior Scales [27]; RSSS: Rett Syndrome Severity Scale [35]; +: Described; -: Undescribed

Table 2: Characteristics of the participants.

Study Design

In the earliest three studies, responses to verbal instructions were assessed [25,26,29]. Djukic et al. presented two or three pictures on a monitor [30,31]. In their design, verbal instructions were limited to the prompt “Look at the TV,” which was used at the beginning of the session. Two studies used a visual paired-comparison (VPC) paradigm [32,33], in which two identical stimuli are presented briefly for familiarization and then the familiar stimuli and a new one are paired on test; recognition is inferred from preferential looking at the new target [20,36,37]. To examine the effect of longitudinal habilitation intervention, the length of fixation in two tasks (tasks 1 and 2) was recorded four times at the start of intervention and at 1, 2, and 3 weeks later [34]. In many studies, visual stimuli were presented for 5 s [25,29-31,34]. Velloso et al. used a permanence of 3 s for the mediator boards and 4 s for the boards that contained the solicited concepts [26]. In the VPC paradigm, 10 s and 5 s were used, respectively [32,33].

Eye-tracking technology

An eye-tracking system was used to record a subject’s visual scanning response (device) and to generate eye-found flag, gaze point, or eyeball position (software). Two studies [25,29] used Eyegaze and Passive Gaze Tracing (LC Technologies, Sao Paulo, Brazil). The other studies used Tobii Eye Tracker and software (Tobii Technology AB, Danderyd, Sweden) [26,30-34]. The participants were seated in their parents’ lap or seating system to minimize body and head movements. They were seated 20-65 cm away from the monitor (monitor size: 15-23 inches).

Data analysis parameters

In four studies [25,26,29,34], the length of fixation to the area of interest (AOI) was used. The other studies included both the length of fixation and number of fixations [30-33]. Total looking time and gaze dispersion were also used as assessment parameters in two studies [32-33].

Primary Findings of Interest

The first eye-tracker study in RTT subjects suggested that girls with RTT can respond to simple commands in a consistent manner [25]. They also seem to present a consistent performance when executing cognitive tasks such as matching pairs and categorizing objects. Eye gaze did not recognize the concepts relative to color, i.e., “red,” “yellow,” and “blue;” shape, i.e., “square,” “circle,” and “triangle;” size, i.e., “big” and “small;” and spatial position “over” and “under” [26]. One study [29] demonstrated that both epilepsy features (age at seizure onset and seizure frequency) and electroencephalography (EEG) characteristics (EEG stage and EEG abnormality pattern) are correlated with the ability to recognize and match pairs and categorize semantically with respect to animals and behavioral features, as assessed with VABS [27] and RARS [28]. Subjects with RTT demonstrated a preference for socially weighted stimuli (they looked at people and into people’s eyes) [30] and for novel and salient stimuli in a way that normally developing children do [31]. Individuals with RTT could recognize faces and patterns; however, compared with age-matched comparison subjects, their recognition was poorer [32]. RTT subjects had difficulty recognizing most expressions and their performance was significantly poorer than that of a TD age- and gender-matched comparison group and had atypical scanpaths-they looked less, had fewer fixations, and often totally ignored key facial features, particularly the mouth [33]. Scanpaths and recognition were also related in RTT participants, with better recognition tied to greater attention to emotion-relevant features. The pattern of fixation duration to experimental tasks was improved after longitudinal habilitation intervention for 3 weeks compared with before intervention [34].

Discussion

This review demonstrated the considerable wealth of eye-tracker data for individuals with RTT published to date. An eye-tracking system is advantageous in that it represents a safe method, while it does not require strict motion restriction, and as a result, it can be used in natural environments. In the reviewed studies, the participants were seated in their parents’ lap or seating system to minimize body and head movements. Despite the use of different visual stimuli paradigms and eye-tracking instruments, several robust and coherent findings emerge regarding eye gaze detected with an eye-tracker system.

The evaluation of cognitive functions and assessment of developmental levels in children almost always depend on verbal or gesture responses, and are focused on the knowledge that the child acquires about the material world [38]. The means of expression of individuals with RTT are limited [39]. Therefore, care staff and family members might attempt to determine whether behaviors such as body movements, vocalizations, eye gaze, and facial expressions serve a communicative function for individuals with RTT or other similarly severe disorders [6]. Girls and women with RTT have been able to use eye gaze to express their will, communicate, learn about the world, and interact with their surroundings [7-22]. This ability has been based on analysis of observations or videotaped sessions, subjective impressions, or assumptions by family members and care staff.

Eye-tracking technology allows the measurement of how long individuals with RTT focus on a stimulus and how many times they fixate on each of the simultaneously presented visual targets. Eye-tracker has been used to assess intentionality [25], to recognize the concepts relative to color, i.e., “red,” “yellow,” and “blue;” shapes, i.e., “square,” “circle,” and “triangle;” size, i.e., “big” and “small;” and spatial position, i.e., “over” and “under” [26], to delineate if and how neurological and neurophysiological impairments reflect behavioral and neuropsychological functions [29], to examine nonverbal cognitive social abilities [30], to demonstrate a preference for novel and salient stimuli in a way that TD children do [31], to study attention and recognition memory in RTT [32], to look at the ability of RTT participants to recognize facial expressions [33], and to evaluate fixation duration changes in an individual with RTT associated with longitudinal habilitation intervention by care staff [34]. This suggests that an eye-tracker is useful to evaluate cognitive function, judge habilitation intervention, and demonstrate a strict correlation between neurophysiological features and neuropsychological impairment.

Of the eight studies reviewed, six provided the personal characteristics of individuals with RTT [25,26,29,32-34]. These results suggest that participants' characteristics should be given to know detailed personal information, to analyze the correlation between eye-tracking data and personal characteristics, and to compare with participants' features in other studies. Four studies included control subjects as a comparison group for the characteristics of TD female participants [30-33]. One study was a case report that used a longitudinal design [34]; therefore, family members and care staff could appreciate the longitudinal changes in the subject.

The major methodological difference was related to the nature of the verbal instruction. In the earliest three studies [25,26,29], eye gaze response to a verbal instruction was designed to assess intentionality [25,29] or recognition of the concepts of color, shape, size, and spatial position [26]. The nature of this verbal instruction, including the requirement for semantic processing (e.g., look at the same, look at the similar, look under), limited the ability of the authors to separate the confounding effects of possibly impaired receptive language abilities on the reported results [29]. In the other studies [30-33], verbal instructions were limited to the prompt "Look at the TV," which was used at the beginning of the session. Verbal instruction for the stimuli should be determined for the purpose of each study because difficulties may arise when interpreting the meaning of the data.

Of the eight studies reviewed, seven presented each picture or stimuli on the monitor for 5 s [25,29-31,34]. Velloso et al. used a permanence of 3 s for the mediator boards and 4 s for the boards containing the solicited concepts [26]. In the VPC paradigm, 10 s and 5 s were used, respectively [32,33]. We suspect that an individual with RTT may not notice a visual stimulus on a monitor when it is presented for a short period of time; however, if it is presented for a long time, her attention may wander from the display. A longer exposure to the stimuli may comprise one of the factors contributing to the different conclusions about the cognitive competence of individuals with RTT [31]. Therefore, the viewing time of visual stimuli or tasks should be considered based on the purpose of each study.

In two recent studies, the VPC paradigm was used [32,33]. This paradigm has also been used in previous studies [20,36,37]. Visually based techniques, such as the VPC, open a new avenue for quantifying the cognitive phenotype associated with this syndrome [32]. If visual stimuli with an eye-tracking system are the same or similar to the stimuli used in previous studies, we can confirm and compare the data. The pedagogic tasks used should also be rethought, in such a way that, in fact, the passive development skills of RTT children are stimulated [26].

In 2009, it seemed appropriate to recommend an increase of objective studies to evaluate, through visual tracking, cognitive concepts in children with RTT, using new interventions and re-evaluations [26]. Hirano et al. used an eye-tracker to evaluate fixation duration changes in an individual with RTT associated with longitudinal habilitation intervention by care staff [34]. Fixation duration to the experimental targets was significantly improved after intervention for 3 weeks compared with before intervention [34]. A previous study reported that continuous instruction from care staff resulted in an individual with quadriplegia, mental retardation, and epilepsy acquiring new upper extremity motions that caused changes in prefrontal brain activation [39]. It has recently been shown that individuals with RTT are able to learn by intervention [40-43]. These findings suggest that individuals with severe motor and intellectual disabilities can acquire various abilities. Quantifiable aspects of eye-tracking have also been used as an outcome measure in studies of autism [44-46].

All reviewed studies used length of fixation and AOIs for analyses. The number of fixations, total looking time, and gaze dispersion were used as assessment parameters in eye-tracking studies. However, the meanings of these parameters have not been discussed sufficiently. We cannot judge which assessment parameters should be used; however, we can compare the data when interpreting the respective parameters and behaviors.

- The use of an eye-tracking system has enabled us to show the following abilities and make suggestions about RTT subjects:
- There is measurable and intentional gaze in RTT girls that can be used as a tool to explore their cognitive performance [25].
- Children with RTT do not indicate recognition of the required concepts with their eyes [26].
- Neurophysiological features should be considered prognostic of cognitive and behavioral outcome in the clinical management of RTT [29].
- RTT subjects demonstrate a preference for socially weighted stimuli (they looked at people and into people's eyes) [30] and for novel and salient stimuli [31].
- RTT subjects can recognize faces and patterns; however, compared with age-matched comparison participants, their recognition was poorer [32].
- Individuals with RTT have difficulty reading emotional expressions and these problems are linked to atypicalities in scanning [33].
- Individuals with RTT can acquire various abilities using eye gaze [34].

The first use of an eye-tracker in RTT participants was to assess their intentionality [25]. This ability had been described previously based on subjective impressions [11,17,20]. An eye-tracker remains highly useful for the evaluation of eye gaze in individuals with cerebral palsy [47].

Individuals with RTT are usually nonverbal and demonstrate a very limited ability to use their hands. Eye tracking represents a feasible method to assess cognition and provide insights into the burden of isolation, the "hidden" abilities of the cognitive world of individuals with RTT [30-32], and to visualize the learning abilities of RTT subjects and judge the outcome of habilitation intervention [34]. Future investigations focused on the correlation between neurophysiological features and definite phases of information processing, attention, memory, and logic relationships in RTT are needed to correlate in more depth the exact stage of information processing impairment with neurophysiological features [29]. Further and more comprehensive studies, including adaptations of standardized neuropsychologic tests and intervention strategies to allow individuals with RTT to reply by looking at instead of saying or pointing to the correct answer, are needed to define cognitive profiles more accurately in this population [30,31]. Future studies with this population would benefit from additional comparison groups, such as a TD group matched for developmental level (which would clarify which functional aspects are related to developmental stage and which are symptom-specific) [32]. More long-term intervention studies are needed to check a participant's longitudinal changes and to identify intervention outcomes [34]. Future studies might enhance the complexity still further, and the use of an eye-tracking system for individuals with RTT could be an effective assistive technology for the integration, adaptation, and neutralization of the environmental barrier [24]. Because we limited to an English articles in this review, other linguistic documents could not refer. We worry whether true meaning of each article was understood.

Conclusion

This review demonstrated the significant progress that has been made in researching eye gaze associated with visual stimuli and tasks for individuals with RTT using an eye-tracker. The reviewed studies could enable family members and care staff to identify intentionality, recognition, preference, attention, the strict correlation between neurophysiological features and neuropsychological impairment, and habilitation intervention outcomes. We suggest that the findings obtained by this technique are utilized to evaluate and examine habilitation plans and means, to judge intervention outcomes, and to determine the correlation between features and impairments and are of significant benefit to individuals with RTT.

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