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Short Review

A Narrative Review on the Use of Eye-Tracking in Rett Syndrome: Implications for Diagnosis and Treatment

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Abstract

Rett syndrome (RTT) is a rare neurodevelopmental disorder primarily affecting females, characterized by a spectrum of debilitating symptoms that impact neurological, cognitive, and motor functions. Eye-tracking technology (ETT) has emerged as a prominent tool in Augmentative and Alternative Communication (AAC) systems, particularly for neurological patients with motor and verbal impairments. This narrative review aimed to evaluate studies conducted on the use of ETT to improve cognitive abilities in girls with RTT and to examine its potential application. A review of the most recent empirical evidences was conducted. Some relevant contributions were highlighted and some useful ideas were detailed. Guidelines for research and practice were argued. The analyzed data demonstrated ETT's effectiveness in improving cognitive abilities in girls with RTT. ETT may be helpful in enhancing cognitive functioning in RTT individuals.

Keywords

Eye tracking; Rett syndrome; cognitive training; assessment; rehabilitation

1. Introduction

RTT is a rare neurodevelopmental disorder primarily affecting females, characterized by a spectrum of debilitating symptoms that impact neurological, cognitive, and motor functions. This syndrome, initially described by Andreas Rett [1], is primarily caused by mutations in the methyl-CpG-binding protein 2 (MECP2) gene located on the X chromosome. The MECP2 gene plays a crucial role in regulating the expression of other genes and is pivotal in brain development and function.

The genetic basis of RTT predominantly involves sporadic mutations in the MECP2 gene, although other genes, such as CDKL5 and FOXG1, have been associated with atypical forms of the disorder. Most cases arise from mutations occurring randomly and are not inherited from parents. These mutations typically lead to a loss of normal MECP2 function or production of a dysfunctional protein, contributing to the clinical manifestations observed in affected individuals [2].

De novo mutations in RTT are almost exclusively of paternal origin, likely contributing to the high female-to-male ratio observed in patients [3]. RTT occurs in approximately 1 in 10,000 to 15,000 live female births globally, making it a relatively rare condition [4]. While predominantly identified in females due to the X-linked nature of the MECP2 gene mutation, cases of RTT in males have been reported [5].

1.1 Consequences on Intellectual, Functional, and Social Levels

Persons with RTT experience a range of neurological impairments affecting both motor and cognitive functions. RTT is characterized by a progressive decline in intellectual, communicative, and motor skills, typically between 5 and 18 months after an apparent normal birth and initial regular development. The syndrome commonly unfolds across four primary stages: (1) stagnation, (2) regression, (3) stationary, and (4) deterioration in motor function [6].

The initial stage (stagnation) marks an arrest in the child's development, typically around 5–6 months. The subsequent stage (regression) normally emerges between 1 and 4 years old, involving a loss of previously acquired skills like language and social interaction. However, the ability to communicate eye contact is preserved [7].

As the syndrome progresses to the third stage (stationary), repetitive hand movements (e.g., clapping, mouthing, washing), breathing irregularities (e.g., hyperventilation), and behavioral disturbances (e.g., nighttime laughing and crying episodes) become noticeable [8]. Additionally, between the ages of 2 and 10 years old, features like apraxia, motor scoliosis, impairments, and seizures are observed [9].

The final stage (motor deterioration) typically has an onset after the age of 10 years, which is marked by a decline in physical abilities, reduced mobility, and a decrease in repetitive hand movements [10].

The diagnostic criteria revised by Neul et al. [11] include severe intellectual disability and/or profound, progressive decline in adaptive abilities, inability to locomotion, communication deficits, and social withdrawal. In RTT, eye gaze emerges as a predominant expressive modality, although it lacks sustained attentional control [12].

1.2 Eye Tracking

Eye-tracking (ET) techniques have emerged as prominent tools in AAC systems, particularly for neurological patients with motor-verbal impairments. These techniques have been extensively used in administering neuropsychological tests, providing a viable means for visually selecting and responding to tasks when motor-verbal capabilities are limited [13].

ETT employs specialized cameras and software, providing a comprehensive analysis of an individual's ocular movements and patterns, enabling the accurate interpretation of their gaze behavior and information processing [14].

In RTT, a neurodevelopmental disorder characterized by motor impairments and communication challenges, ETT is an invaluable tool for facilitating interactions and communication. These systems empower persons with RTT, who may face motor limitations, to utilize their gaze to control interfaces, express choices, and access the technology. By accurately capturing and interpreting eye movements, these technologies offer a crucial pathway for AAC, enabling individuals with RTT to express themselves, make informed decisions, and constructively engage with their surroundings. A recent study [15] found a positive effect on brain activation and communication using ETT and AAC during cognitive stimulation.

ETT showed efficacy in cognitive and emotional impairments in various neurological, neurodevelopmental, and psychiatric disorders. The importance of gaze-contingent ETT training for improving attentional functions and the use of eye behaviors for assessing cognitive and emotional states across different clinical populations were emphasized. Interventions comprising gaze-contingent training programs focusing on attention, inhibition, and visual memory enhancement, such as attention control training, inhibitory ability improvement, and interactive digital gaming, were included [16, 17].

ETT can improve communication, quality, and reliability in cognitive assessment for children with severe motor and communication impairments [18]. The clinical diagnostic framework commonly involves motor coordination difficulties and verbal communication challenges.

ETT can be used for (a) assessing visual abilities, monitoring eye movements helps evaluate a person’s ability to track objects, individuals, or visual stimuli despite RTT's limitations [19], (b) assessing cognitive abilities, eye tracking can provide a comprehensive evaluation of cognitive abilities in RTT, potentially improving intervention and support service options [20], (c) non-verbal communication, if RTT restricts verbal communication, eye tracking enables individuals to communicate by selecting objects or symbols on a screen using eye movements [21], and (d) tracking changes over the time, comparing eye tracking data at different intervals helps monitor the progression of RTT, assessing improvements or deteriorations in visual and motor abilities. Thus, some studies demonstrate its potential in evaluating cognitive function, habilitation results, and language understanding [18, 22].

Fabio, Giannatiempo, Semino, and Caprì [23] examined longitudinal effects of cognitive rehabilitation in persons with RTT, which exhibit long-term improvements in some specific regions, such as attention span and the number of choice behaviors they exhibit.

This narrative review aimed to synthesize and compare existing research on cognitive evaluation and rehabilitation for persons diagnosed with RTT using ETT. The aim was to present a comprehensive summary of successful approaches and advancements in clinical application and perspective investigation.

2. Method

A computerized search was performed in SCOPUS. The eligibility criteria were (a) range interval 2017-2023, (b) limited to publications in the English language, and (c) empirical studies involving at least one participant diagnosed with RTT without age restrictions. The keywords merged were: eye tracking, RTT cognitive training, treatment, assessment, and rehabilitation.

The database was queried by entering the following strings:

(a) (eye AND tracking; syndrome AND Rett; cognitive AND training) Two records were found, and one study was excluded because it investigated the motor training;

(b) (eye AND tracking; syndrome AND Rett; rehabilitation): Three records were found, and all were included in the review;

(c) (eye AND tracking; syndrome AND Rett; cognitive AND assessment): Seven records were found, and, four were included, and one record featuring a participant with Angelman Syndrome was excluded from consideration. Two records were excluded because exploring the assessment of oculomotor function. One record was excluded because it investigated motor training.

The search was focused on the analysis of documents that included persons diagnosed with RTT undergoing evaluation and cognitive training utilizing eye-tracking techniques. Eight papers were reviewed accordingly.

2.1 Narrative Review

This narrative review aimed to summarize and compare the current literature on cognitive assessment and training or rehabilitation in persons diagnosed with RTT through EET to provide an overview of effective strategies and successful improvements in clinical practice and future research. The novelty features may include (a) the newest empirical studies on this specific topic and (b) targeting comprehensive assessment and rehabilitative strategies.

Migliorelli et al. [24] showed substantial changes in brain rhythms during and after cognitive stimulation, indicating that the effects of the stimulation may be extended to the brain’s activity after it ended. In this study, a portable eye-tracking device, the Tobii Dynavox PCEye Explore, was utilized. It was employed much like a computer mouse, enabling users to navigate and control the computer by monitoring their gaze. The experimental protocol involved a 30-minute duration of EEG data collection, which included: (1) Baseline (3 minutes): EEG recording with open eyes; (2) Initial stage (7 minutes): featuring the presentation of an audiovisual distractor; (3) Intervention (10 minutes): participants performed cognitive tasks using the Look to Learn software from Smartbox Assistive Technology; and (4) Final stage (10 minutes): an audiovisual distractor was again presented.

Results could support functional interconnectedness in response to cognitive stimulation observed in RTT individuals. They demonstrated the utility of EEG measurements as biomarkers for categorizing RTT severity and for the objective assessment of cognitive tasks as well as other potential remedies like electrical stimulation or medication.

Topographical significance probability maps showed that the cognitive task was connected with statistically significant decreases in delta activity and increases in beta rhythm. Entropy increased during and after the task, probably due to more complex brain activity. The Brain Symmetry Index

(BSI) positively remarkably correlated with age, showing that younger girls (ages 5-10) had more pronounced augmentation of interhemispheric symmetry.

Ward, Chiat, and Townend [25] used ETT to analyze and compare the performance of children with RTT in newly developed formal and informal examinations on language and cognition. This study focused on Visual Reception (VR) and Receptive Language (RL). Participants were assessed using the Mullen Scales of Early Learning for use with eye gaze technology (MSEL-A/ET), while regular MSEL assessments were used for Expressive Language (EL). Formal and informal assessments were used, tasks were organized according to MSEL categories, and an observation sheet was used for informal assessments. The study recognized the limitation of the upper age limit in the standard scoring mechanism of the MSEL.

Before the assessment session, participants' experiences with using eye gaze technology for communication were diverse. Seven individuals possessed their devices, while three did not. Among those who used their own devices, two or three primarily used them for recreational purposes, such as games, before transitioning to using them as communication tools. Others had immediate access to their devices for communication purposes upon receiving them. The availability of devices varied throughout the day and across different settings, encompassing home, school, and outdoor environments. Moreover, a range of vocabulary systems were utilized, featuring various grid sizes and page types, including core and fringe vocabulary pages and topic and phrase-based pages. Two participants also used a reliable, low-tech paper-based communication system.

Additionally, tasks like reading and cake decorating included informal evaluations of such skills. The comparison between informal and formal assessments revealed mixed results, indicating that people have different preferences and response patterns. While some children performed better on formal tasks, others performed better on casual tasks.

Ahonniska-Assa et al. [18] explored whether employing ETT in forced-choice tasks could provide a means for children facing significant motor and speech limitations to consistently respond, facilitating a more dependable assessment of their language comprehension. This intervention integrated ETT in two key ways: to enhance communication skills through engaging computer games. Secondly, the Peabody Picture Vocabulary Test-4 (PPVT-4) is used to assess receptive vocabulary.

Participants exhibited diverse performance levels on the PPVT-4, ranging from low-average to severe cognitive impairment.

Among four options, participants selected the matching picture for a verbally presented target word. The task was adapted for the My Tobii PCEye tracking device, which used compatible grid software. Pictures were displayed on a screen, and one correct image was placed randomly. Participants confirmed picture scanning by fixating on each image, signaled by a red frame. After confirmation, the target word was announced, and participants located the corresponding picture. The screen was divided into quarters with spaced options for adequate fixation. A green frame indicated a completed choice once fixation exceeded baseline time. The examiner verified the choice's intentionality, with participants responding "yes" or "no." If affirmative, the next question was presented; if negative, a second trial was provided.

Although not all participants demonstrated sufficient motivation to engage with eye-gaze technology for communication purposes, a noteworthy outcome of the present study was that at least half of the participants experienced positive outcomes in learning to utilize ETT for communication during gaming activities and assessment sessions. Young age at the time of assessment was positively correlated with higher receptive vocabulary.

Iannizzotto, Nucita, Fabio, Caprì, and Lo Bello [26] improved the more common chat and teleconferencing programs by adding the capability to determine the direction of users' gaze remotely.

The authors implemented a program named Speak with Your Gaze (SWYG), composed of four modules: the Video Acquisition Module (VAM), the Face Detection and Analysis Module (FADAM), Eye-Gaze Tracking Module (EGTM), and the Visualization Module (VM).

SWYG did not need to be installed on the child's computer; it operates on the "operator" side of the connection alongside the videoconferencing software. The chosen option could be selected by the participant just by keeping their eyes fixed on it. It provided the operator with an automated indication of the participant’s eye-looked direction and enhanced communication. Communication improvements were observed.

Vessoyan, Steckle, Easton, Nichols, Mok Siu, and McDougall [21], in a case series including four participants, determined that using eye-tracking technology to access a speech-generating device (SGD) with dynamic display (TobiiTM1 SGD) using Grid 2T or Communicator 4TM was appropriate.

The study investigated the benefits of utilizing ETT for, accompanied by continuous assistance from a team of AAC therapists, to assist four individuals diagnosed with RTT in achieving personalized communication objectives. Two additional goals were explored parents’ viewpoints regarding (a) the psychosocial consequences of their child’s utilization of the technology and (b) their satisfaction with respect to the use of technology.

Parents showed a great deal of satisfaction with the device as well as the medical care they got. This study supported initial evidence for the effectiveness of eye-tracking as a valuable and potentially rewarding technique to support communication in people with Rett syndrome.

Dovigo et al. [27], during the COVID-19 pandemic, integrated Interactive School palimpsest moments in which teachers spoke with RTT students and waited for an eye gaze response, as well as breaks in which tale cartoons were shown while keeping a watch on the students’ eye gaze.

The squared areas of interest (AOI) were centered around the target. They were sized to encompass a visual field of approximately 19 degrees.

The fixation length (FL) was measured for each AOI corresponding to each stimulus, indicating the duration (in seconds) the participants devoted to fixing the target.

Regarding social interactions, after an opening multimedia presentation, participants were individually spotlighted on video and encouraged to introduce themselves based on their abilities. Cognitive interactions included the presentation of cartoon segments extracted from popular movies, such as “Heide,” “Minnie,” and “Mary Poppins,” tailored for comprehension. Each cartoon segment lasted 2:30 minutes, followed by a recognition test consisting of 10 questions about the story, with two picture options for each question. Participants were scored based on choosing the correct answer, with the session lasting approximately 20 minutes.

Children who participated in social and cognitive tasks showed increased attention and decreased stereotypy.

3. Discussion

The reviewed studies evidenced critical new understandings of how assessment and cognitive training programs could affect brain functioning in individuals with RTT [24]. The observed alterations in brain activity patterns, either during or following cognitive stimulation, point to a valuable direction for more studies and the creation of therapies devoted to improving the mental and communicative abilities of persons with RTT.

Establishing a cognitive training system offers a promising avenue for individuals with RTT, even in purposeful language loss [28]. Integrating such systems into rehabilitation programs aligns with understanding the interconnected relationship between cognitive and motor functions, fostering improved communication and overall well-being.

Individuals with RTT may have different motor impairments and experience various levels of motor functioning. The interrelated connection between attention and motor systems offers valuable insights that can be applied practically in developing motor rehabilitation programs tailored for persons with RTT syndrome [29, 30]. Assessments and interventions must be adapted to accommodate these variations, ensuring that the activities are engaging and achievable for each person. Individualized approaches to assessment and intervention are mandatory for people with RTT, as they have unique preferences and capabilities in different contexts [25].

Persons with RTT may have different communication abilities and modes. Adapting interventions based on an person's preferred communication method, whether it be through gestures, eye movements, or other non-verbal cues, enhances the likelihood of successful communication interactions [31]. As suggested by Rose et al. [32], combined with non-verbal tasks, ETT promises to reveal the cognitive abilities of individuals with RTT.

Applying ETT to enable participants to operate speech-generating devices represents an innovative solution that appears to hold substantial promises, specifically in light of the motor impairments associated with RTT [33, 34]. Besides allowing persons with RTT to express themselves through communication devices, ETT addresses the specific challenges posed by motor difficulties in traditional modes of interaction.

A comprehensive understanding of contextual and motor-related elements and influencing gaze behavior may help improve comprehension of social interaction skills in RTT. Furthermore, it may be helpful to provide opportunities for the development of more efficient and personalized interventions that cater to the specific needs of persons with this diagnosis [12].

Adapting interventions based on a person's preferred communication method is crucial for person-centered care. Additionally, such interventions should be highly customized and tailored to the person’s characteristics and needs to conceptualize individual differences. Finally, an individualized program enhances more successful, meaningful, and positive communication interactions, which in turn improves the person's overall quality of life and may reduce caregivers’ and families’ burdens.

Overall, integrating Eye-Tracking technology with traditional cognitive interventions for persons with RTT represents a promising approach to enhancing mental and emotional training outcomes, offering a valuable tool for therapists and researchers [17].

4. Conclusion

This narrative review provided a general picture of the latest empirical studies exploring ETT application for assessment and rehabilitation in individuals with RTT. Encouraging outcomes have emerged, particularly in the cognitive realm, with notable improvement in language and attention domains. The positive findings underscore the potential of ETT as a valuable tool in addressing cognitive challenges associated with RTT syndrome.

A limitation of the study is related to the small size of participants in the analyzed studies, although this can be explained as RTT is a rare genetic disease. Nonetheless, the small size of participants undergoing ETT training does not allow for the generalizability of the results.

To advance the research field, future research endeavors should focus on developing and implementing protocols incorporating ETT into comprehensive cognitive and motor training programs, enhancing our understanding and refining interventions for individuals with RTT.

Additionally, future research should focus on integrating many immersive technologies, such as virtual reality, into cognitive training programs tailored for people with RTT. This study would entail exploring and incorporating diverse experiential realms to enhance the effectiveness of the training.

Furthermore, one may argue for combining ETT and assistive technology-based programs to ensure individuals with RTT literacy access. Serious games integrated with ETT might enhance social and cognitive skills further. Eventually, low-technology-based tools can be included and integrated with ETT. Matching and integrating different technological systems may be an invaluable teaching strategy. Finally, artificial intelligence systems may be embedded based on reinforcement learning principles to customize high technological solutions [35-39].

Author Contributions

AP conceived and drafted the paper. AZ, MDG, and EC edited and revised the paper. FS critically revised the manuscript. All the authors approved the final version and made a substantial contribution to the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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