



Original Article

Rett Syndrome: Basic Features of Visual Processing—A Pilot Study of Eye-Tracking

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ABSTRACT

Consistently observed “strong eye gaze” has not been validated as a means of communication in girls with Rett syndrome, ubiquitously affected by apraxia, unable to reply either verbally or manually to questions during formal psychologic assessment. We examined nonverbal cognitive abilities and basic features of visual processing (visual discrimination attention/memory) by analyzing patterns of visual fixation in 44 girls with Rett syndrome, compared with typical control subjects. To determine features of visual fixation patterns, multiple pictures (with the location of the salient and presence/absence of novel stimuli as variables) were presented on the screen of a TS120 eye-tracker. Of the 44, 35 (80%) calibrated and exhibited meaningful patterns of visual fixation. They looked longer at salient stimuli (cartoon, 2.8 ± 2 seconds S.D., vs shape, 0.9 ± 1.2 seconds S.D.; $P = 0.02$), 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 seconds S.D. vs 1.8 ± 1 seconds S.D., $P = 0.002$). Eye-tracking provides a feasible method for cognitive assessment and new insights into the “hidden” abilities of individuals with Rett syndrome.

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Introduction

Rett syndrome is a severe, X-linked disorder of neuro-development, caused by mutations in the methyl-cytosine-phosphate-guanine binding protein 2 (*MECP2*) gene located on Xq28, first described in 1966 [1,2]. Profound impairments in the ability to speak, walk, and use hands, caused by apraxia and movement disorder, severely limit the abilities of girls with Rett syndrome to reply to questions during standardized neuropsychologic testing, and thus may have led to underestimations of their cognitive abilities [3,4].

Vision and gaze are considered the most important ways in which girls with Rett syndrome relate to the world [5,6]. Numerous observations in the literature contend that these girls demonstrate strong eye gaze, eye contact, and visual tracking [7–9], and almost uniform reports by parents and caretakers state that these girls use eye gaze to greet, point, request, and refuse. However, the approach best suited for the assessment of cognitive function in girls with Rett syndrome remains unclear [10,11].

The specific aims of this pilot study were:

- (1) To determine the basic features of nonverbal cognitive processes in girls with Rett syndrome, such as characteristics of their visual fixation pattern (meaningful vs random) and visual attention (in response to novelty); and
- (2) To determine the feasibility of eye-tracking as a method for cognitive assessment in girls with Rett syndrome.

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Study Design and Methods

This study was performed in 44 consecutive female patients with the typical form of Rett syndrome (which was also genetically confirmed; mean age, 10 ± 6 years S.D.) [12]. Good eye contact was present in 34 (78%) girls with Rett syndrome, and nonverbal communication (intentional eye or hand pointing) was present in 32 (74%) girls with Rett syndrome. Only eight (18%) girls were able to execute some purposeful movements with their hands (such as manipulating switches or toys, or eating with utensils).

Nine girls were not able to complete the test. Seven girls exhibited poor joint attention (five were alert but overactive or restless, and two appeared lethargic). Two girls with severe orthopedic deformities (e.g., scoliosis and contractures) could not maintain the testing position because of discomfort. These girls were excluded from further study, leaving 35 girls with the typical form of Rett syndrome for further analysis [12].

To determine the characteristics of visual fixation patterns, we presented two pairs of slides on a Tobii Studio 120 eye-tracking device (Tobii Technology, Danderyd, Sweden) with Enterprise software (Figs 1 and 2). Noninvasive, wireless, near-infrared illumination was used to record reflection patterns on the cornea and pupils while the girls were looking at the presented pictures [13]. The eye tracker measures characteristics of the patient's eyes, and uses them together with an internal,

physiologic three-dimensional eye model to calculate gaze data. Each picture was presented for 5 seconds. The study was performed with lights on. Girls were seated 30–50 cm away from the monitor. Verbal instructions were limited to the prompt “Look at the TV,” which was used at the beginning of the session. To minimize body and head movements, subjects were seated in their parents' laps. Parents kept their eyes closed during testing.

The first pair of slides (Fig 1A,B) was used to determine whether girls with Rett syndrome demonstrate the ability to discriminate visual stimuli by their salience. The difference between the two images within this set of slides involved the position of the salient (cartoon) character, which was placed at the top on slide A, and at the bottom on slide B.

To determine whether girls with Rett syndrome exhibited any preference for novel stimuli, we presented the pair of slides depicted in Fig 2. Within this pair, the central figure (giraffe) appeared on both slides. The difference between the two slides involved the absence or presence of the novel stimuli, which were depicted only in slide B.

To determine whether girls with Rett syndrome demonstrate the ability to identify and focus on salient visual stimuli (i.e., the recognition of a cartoon character vs a shape) and novel visual stimuli, we measured (1) how long girls with Rett syndrome focused on a stimulus, and (2) how many times they fixated on each of the simultaneously presented visual targets.

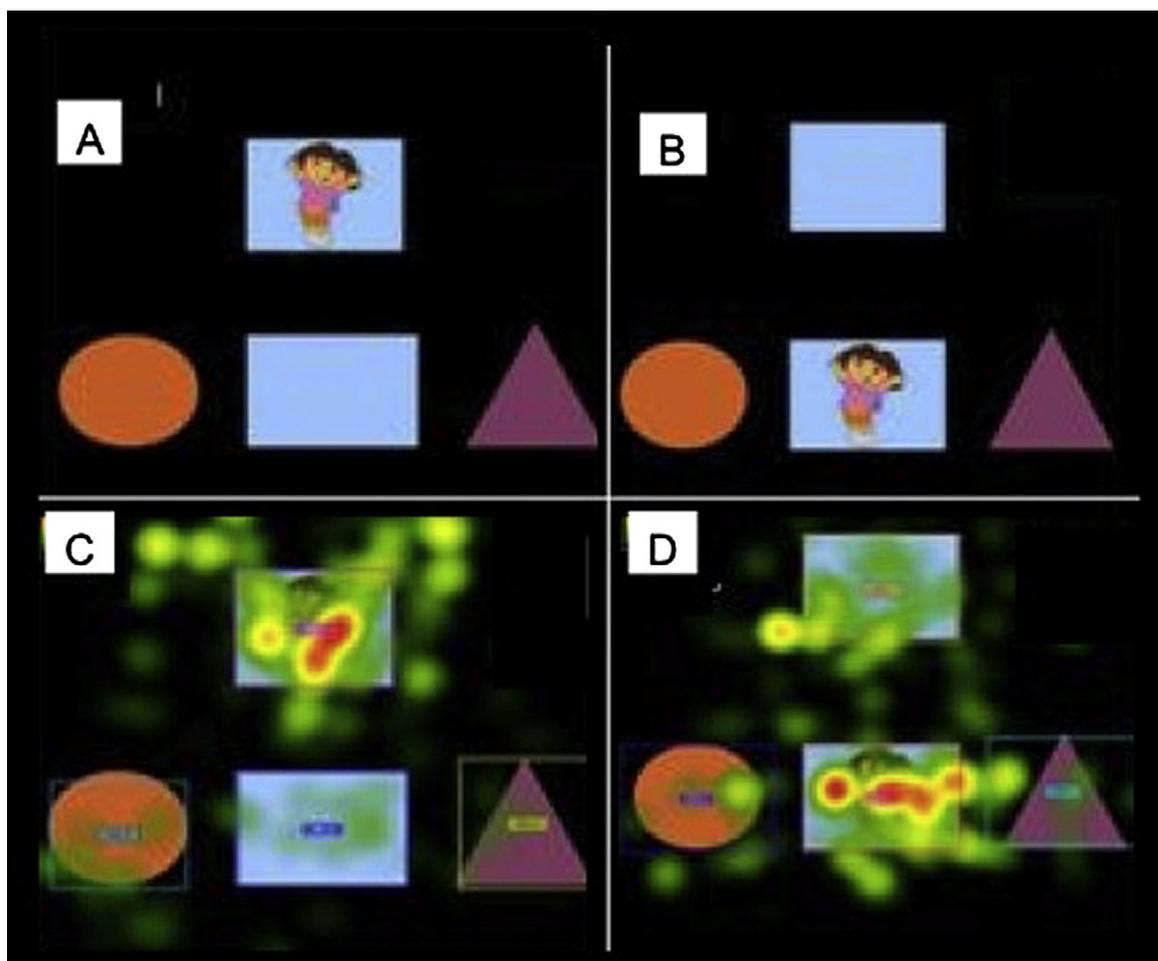


Figure 1. Pattern of visual fixation in girls with Rett syndrome: discrimination of the salience of visual stimuli. (A and B) Slides depict changes in the position of the salient stimulus (i.e., the cartoon character Dora). Areas of interest used for data analysis are marked by squares. (C and D) “Heat maps” are presented as a way to visualize eye-tracking. A heat map uses different colors to indicate the amount of fixations in certain areas of the presented pictures. Warm colors (red) indicate areas where the participants fixated for a long time or on many occasions. An area with no color indicates that the participants did not fixate in that area. Girls with Rett syndrome demonstrated a preference for the cartoon over shapes. They identified Dora as the most salient stimulus, and spent the most time on this image, regardless of its position within the slide.

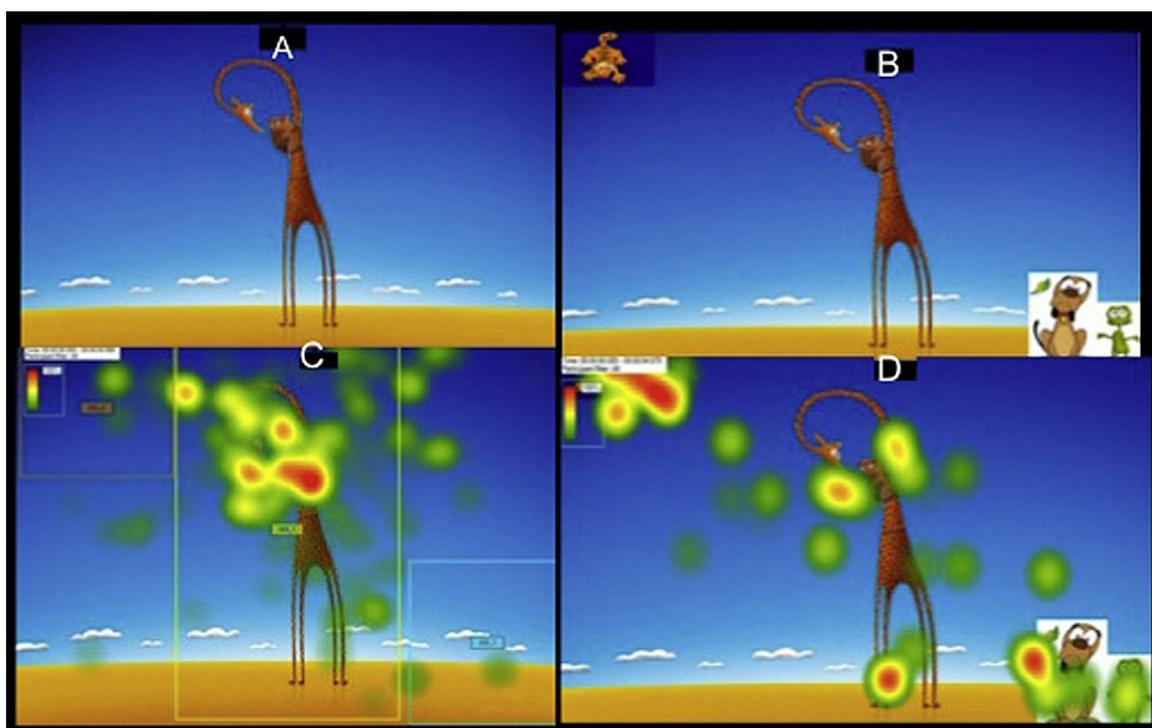


Figure 2. Pattern of visual fixation in girls with Rett syndrome: attention to novelty. (A and B) Slides depict changes in the number of stimuli shown (two novel stimuli added in two corners within slide B). (C and D) The areas of interest used for data analysis, marked by squares, indicate the duration of visual fixation on different areas in the form of “heat maps”. Girls with Rett syndrome demonstrated a preference for novel stimuli. When novel stimuli were introduced, the girls spent less time looking at the figure (giraffe) they had previously seen.

Findings were compared with those in a group of 33 typical female control subjects (mean age, 12.2 ± 6.5 years S.D.). The data are presented as means \pm standard deviations and as frequencies, and were analyzed according to the *t* test, χ^2 test, nonparametric tests, and analyses of covariances. The Montefiore-Einstein Institutional Review Board approved this study.

Results

Girls with typical Rett syndrome who were able to complete testing exhibited meaningful patterns of visual fixation when multiple stimuli were presented simultaneously. Salience of the visual stimuli was the single most important determinant of the pattern of their visual fixation. They looked at the same location within the slide significantly more often (4.8 ± 4 times S.D. vs 2.5 ± 3 times S.D., $P = 0.06$) and longer (2.8 ± 2 seconds S.D. vs 0.9 ± 1.2 seconds S.D., $P = 0.024$) when a cartoon was presented than when the shape was presented (Fig 1C,D). The girls spent equal amount of time looking at the cartoon regardless of its location on the screen (2.5 ± 1.9 seconds S.D. vs 2.4 ± 1.5 seconds S.D., $P = 0.8$), both when it appeared at the top and when it appeared at the bottom (Fig 2C,D).

Typical control subjects presented similar patterns of visual fixation and looked longer at the cartoon than at the shapes (2.8 ± 1.7 seconds S.D. vs 1.3 ± 0.8 seconds S.D., $P < 0.001$), but girls with Rett syndrome were more likely to look at only one area of the slide (cartoon) than were control subjects (73% vs 4%, $P < 0.001$).

The girls exhibited a preference for novel stimuli over the stimulus they had seen previously, i.e., the giraffe (Fig 2C,D)

After a novel stimulus appeared, their attention shifted toward it, and the number and duration of fixations (in seconds) on the stimulus that was seen previously (giraffe) decreased significantly (duration of fixations, 2.7 ± 1 seconds S.D. vs 1.8 ± 1 seconds S.D., $P = 0.002$; number of fixations, 5.7 ± 3 S.D. vs 4.2 ± 3.3 S.D.; $P = 0.05$).

Control subjects demonstrated a similar preference for novelty, decreasing the duration of fixations when a novel stimulus appeared (duration of fixations, 2.8 ± 1.5 seconds S.D. vs 1.7 ± 1.3 seconds S.D., $P = 0.001$), but did not demonstrate differences in the number of fixations (5.8 ± 3.5 S.D. vs 4.3 ± 3.1 S.D., $P = 0.08$).

Discussion

Girls with Rett syndrome demonstrated a preference for novel and salient stimuli in a way that normally developing children do. These results, together with the results reported in our previous study (that girls with Rett syndrome exhibit exquisite visual preference for socially weighted stimuli, i.e., a preference for looking at people vs objects, regardless of their position on the screen, and a preference for looking into people's eyes), open up new insights about their neurodevelopmental profile and their ability to process and discriminate visual stimuli and relate to the world around them [14].

Eye-tracking methodology similar to ours was used in two previous studies to assess cognition [15,16]. Baptista et al. [15] examined the recognition-matching and categorization of pictures, and concluded that six of seven girls responded

correctly to at least one task. Velloso et al. [16] assessed the recognition of the concepts of color, shape, size, and spatial position in 10 girls with Rett syndrome, and concluded that they did not recognize the required concepts. Aside from sample size, a major difference between these studies and our study is methodologic, i.e., related to the nature of the instruction and the viewing time [15,16]. Velloso et al. [16] limited the viewing time to 3–4 seconds. Longer exposure to the stimuli in our study may comprise one of the factors contributing to different conclusions about the cognitive competence of girls with Rett syndrome in these studies. The second major methodologic difference is related to the nature of the instruction. In Baptista et al. [15] and Velloso et al. [16], the tasks required an eye-gaze response to verbal instructions. 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 to separate the confounding effects of possibly impaired receptive language abilities on the reported results. Thus, difficulties may arise in interpreting the meaning of the data. To allow for the best estimates of accuracy of visuomotor skills/eye pointing, we minimized demands on receptive language skills.

Thirty-five of 44 girls in this study demonstrated a sufficient ability to process visual stimuli, identify the salient stimulus, and focus their eye-gaze on it. When multiple symbols were presented simultaneously, the instinct properties of the stimulus (i.e., the cartoon character Dora) endowed salience by virtue of relevance to the subject. This phase of testing required patients to attend selectively and filter out irrelevant sensory information in favor of relevant information. The consistency with which girls with Rett syndrome performed in this part of the test opens up new insights about their ability to process visual stimuli, involving the presence of meaningful patterns of visual fixation and preferential attention to novelty, in the same way demonstrated by typical children [17,18].

The striking similarities and differences in eye-fixation findings between the Rett cohort and the control subjects are intriguing. The majority (73%) of the Rett cohort tended to focus all of their attention on the cartoon character, to the exclusion of the remainder of the slide (vs only 4% of the control cohort). To answer questions of whether this finding reflects their tendency to be “overly focused” on items of interest, their difficulties in shifting attention, their need for longer viewing times, or some other reason, further and more comprehensive studies are needed.

This study provided important additional information related to several characteristics of the clinical phenotype that appear to be important predictors of eye-gaze performance. Clinical features most discouraging in terms of the patient's ability to be tested by eye-tracking included restlessness and overactivity, poor engagement, limited joint attention, and decreased alertness. Only eight (18%) girls were able to execute some purposeful movements with their hands, leaving the majority (82%) of girls to rely on their eye gaze as the main way of communicating with the world.

We conclude that eye-tracking represents a feasible method for assessing cognition and understanding the interior world of individuals with severe apraxia and a limited repertoire of abilities with which to express themselves and be tested. Girls with Rett syndrome are usually nonverbal and demonstrate a very limited ability to use their hands. The fact

that characteristics of their eye gaze can be quantified opens the possibility that pointing by looking may be used for testing purposes instead of more conventional verbal replies or manual/finger pointing. Currently, language abilities represent the cornerstone for assessments of cognitive function. Providing girls with Rett syndrome the ability to respond by looking may allow us to gain more realistic insights into their minds, revealing perceptual and cognitive abilities including memory, attention, and receptive language. This pilot study concerned feasibility, and represents only the first step in our efforts to answer the fundamental question of the meaning and nature of the consistently described “strong eye gaze” in individuals with Rett syndrome in an objective and systematic way.

Quantifiable aspects of eye-tracking were used as an outcome measure in studies of autism [19–21]. The results of this study imply that eye-tracking methodology may represent a valuable tool in studies and treatment trials among this population of patients.

Further and more comprehensive studies, including adaptations of standardized neuropsychologic tests to allow girls with Rett syndrome 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.

The authors had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. The acquisition of equipment used in this study was made possible by generous donations to the Rett Center at Montefiore from families of our patients R.R. and J.D. A.D. was supported by the International Rett Syndrome Consortium-RettSearch and the International Rett Syndrome Foundation (through a microgrant mechanism). The participation of C.L.M. in this study was supported by the Hospital Garcia de Orta and the Calouste Gulbenkian Foundation. The authors thank Solomon Moshe, MD, for valuable suggestions during preparation of the manuscript.

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