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Original Article

Impaired Visual Search in Children with Rett Syndrome

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ABSTRACT

Aim: This study aims to investigate selective attention in Rett syndrome, a severely disabling neurodevelopmental disorder caused by mutations in the X-linked *MECP2* gene.
Method: The sample included 28 females with Rett syndrome (RTT) and 32 age-matched typically developing controls. We used a classic search task, in conjunction with eye-tracking technology. Each trial included the target and several distractors. The distractors varied in number and differed from targets in either a "single feature" (color *or* shape), creating a pop-out effect, or in a "conjunction of features" (color *and* shape), requiring serial search. Children searched for the target in arrays containing five or nine objects; trials ended when the target was fixated (or 4000 ms elapsed).
Results: Children with Rett syndrome had more difficulty finding the target than typically developing children in both conditions (success rates less than 50% versus 80%) and their success rates were little influenced by display size or age. Even when successful, children with RTT took significantly longer to respond (392 to 574 ms longer), although saccadic latency differences were observed only in the single-feature condition. Both groups showed the expected slowing of saccadic reaction times for larger arrays in the conjunction-feature condition. Search failures in RTT were not related to symptom severity.
Conclusions: Our findings provide the first evidence that selective attention, the ability to focus on or select a particular element or object in the environment, is compromised by Rett syndrome. They reinforce the notion that gaze-based tasks hold promise for quantifying the cognitive phenotype of RTT.

Introduction

Rett syndrome (RTT), a severely disabling neurodevelopmental disorder that affects about one in 10,000 females,[1] is caused by *de novo* mutations of the x-linked methyl-CpG-binding protein 2(*MECP2*) gene located on the long arm of the X chromosome—Xq28.[2] The *MECP2* gene encodes MeCP2, which is involved in regulating the transcription of other genes, as well as in synaptic development and maintenance.[3] RTT is characterized by apparently normal early growth and development (until about six to 18 months) followed by partial or complete loss of purposeful hand movements and expressive language, along with the appearance of gait abnormalities and stereotypic hand movements.[4,5] Among other frequent symptoms are breathing irregularities, bruxism, seizures, growth retardation, and scoliosis.

Because the profound impairments in speech and motor control in RTT preclude standard neuropsychologic testing, the cognitive phenotype of RTT remains largely unknown. Using eye-tracking technology to by-pass these problems, we recently were able to identify specific deficits in recognition memory in this population,[6-8] along with evidence suggesting that the source of some of these difficulties may lie in impaired attention. In particular, the scanning patterns of these children were often atypical—characterized by looking that was more concentrated in one area of the display and less well distributed across the whole display. These

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[1] Dr. Feldman, who made major contributions to the conceptualization, data analysis, and preliminary write-up of this work, passed away.

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atypical scanning patterns may point to a larger problem, given that attention is a multifaceted construct[9] and is foundational to many areas of cognitive growth.[10-14] To better understand the attentional abilities of children with RTT, we have been examining three core components of this domain: *Sustained attention,* maintaining focus on a target while ignoring distractors;[15] *Disengagement of Attention,* shifting focus while ignoring competing information (in press); and *Selective Attention,* searching the visual field to find a target in an array of distractors. The present report deals with this last aspect.

Models of selective attention have relied heavily on visual search tasks,[16] with task difficulty determined by the nature of the difference between target and distractors. Two conditions are generally juxtaposed: the *single-feature condition* (e.g., red circle among green circles), where the target has a distinctive characteristic that differentiates it from the other stimuli, and the *conjunction-feature condition* (e.g., red circle among green circles and red squares), where the target cannot be distinguished from the distractors by a unique feature, since it shares color with some distractors and shape with others. In the single feature condition, search is generally fast and efficient; with the target tending to "pop out" largely independent of the number of items in the array.[17] In the conjunction-feature condition, search is typically more active, and involves serial scanning, which takes longer with larger arrays.

In the present study, we assessed search behavior in children with RTT, adapting an eye-tracking version of the search task recently developed by Kaldy et al.[18]

Methods

Participants

The sample included females with clinically diagnosed classical Rett syndrome,[5] recruited from the Rett Center at the Children's Hospital of Montefiore, and a comparison group of typically developing females.

The RTT group was a sample of convenience with children recruited at their scheduled visit to the Rett Center. Children were recruited as long as they were neither sleepy nor overactive/restless, nor had any severe orthopedic deformities that would have interfered with maintaining the testing position (e.g., scoliosis or contractures).

The typically developing group, recruited from the outpatient clinics of the same hospital, was drawn from children who were family members of patients with appointments at pediatric specialty clinics; this group excluded children with significant neurological/chromosomal/or neurodevelopmental disorders.

Clinical characteristics of the RTT sample were assessed with the Rett Syndrome Severity Scale (RSSS).[19]

The protocol was approved by the institutional review board and written consent was obtained for all participants.

Apparatus

Stimuli were presented on a 23 inch flat panel monitor (resolution, 1024×768 pixels) in conjunction with a Tobii X2-60 infrared eyetracker (Tobii Technologies). Matlab, Psychtoolbox, and Talk2Tobii software were used to allow for a gaze-contingent interface during stimulus presentation. Manufacturer-supplied algorithms for pupil, corneal reflection, and face identification were used during eye-tracking; gaze data were sampled at 60 Hz. Left and right eye gaze positions were recorded separately and then averaged for analyses.

Procedure

Children were tested in a quiet, dimly lit room, seated approximately 45 cm from the monitor. To minimize body and head movement, children in the RTT group (and all typically developing participants less than five years) were seated on a caregiver's lap. Caregivers kept their eyes closed during testing.

Calibration

At the start of the session, children completed a five-point calibration procedure in which pulsing colored blocks (1° to 1.5°), with accompanying sound, appeared at the center and in the four corners of the monitor, in a randomized order. Point-of-gaze was calibrated by comparing each look to the known coordinates of the target, and results were presented graphically. The quality of the calibration was determined by the closeness of the fixation points to the calibration points. If the points did not cluster, or any targets were missed, the calibration was repeated.

Search task: design and stimuli

The search task, adapted from Kaldy et al.,[18] contrasts single feature and conjunction feature search with varying set sizes. Fixations to the target and distractors are monitored. In our adaptation, the task was made gaze-contingent, with trials ending when the child looked at the target.

All trials started with the presentation of the target stimulus—the red apple (5° visual angle)—which appeared alone in the center of the screen for 1000 ms (emitting an attractive *oh* sound); immediately afterwards the target reappeared, randomly placed among distractors (blue apples; red cylinders). When the child looked to the target (or 4000 ms elapsed), the trial ended and the target spun and made a prolonged *ah* sound.

The entire task consisted of two blocks of trials, each containing four familiarization trials followed by 13 test trials (for a total of 34 trials). In each block, the four familiarization trials were presented first, to acquaint the child with the task and stimuli. For these trials, the red apple was presented along with a blue apple and a red cylinder (the two distractors), with the spatial configuration of the three items varying across trials.

The 13 test trials were presented next, with single- and conjunction-feature trials intermixed. In *single-feature trials*, the distractors differed from the target in one feature (color *or* shape), creating a pop-out effect; in *conjunction-feature trials*, the distractors differed in both features (color *and* shape), and finding the target is thought to require serial search (Fig). Following Kaldy et al. (2011) there were four single-feature trials (two containing five items and two containing nine items) and eight conjunction trials (four containing five items and four containing nine items). In all cases the items presented consisted of one target with the rest being distractors. (Each block also included a single conjunction trial with 13 items, but these trials were dropped from consideration because of too much missing data).

Each block of trials lasted less than two minutes; the blocks were interleaved with other attention tasks in a testing session that, in its entirety, took about 10 min.

Measures: The central measures were (1) number of successful trials (fixating the target within 4000 ms) and (2) reaction time (RT) to find the target on successful trials.

Data analyses

All measures were examined for normality and outliers and then analyzed using a mixed model 2 (Group: RTT versus typically developing) $\times$ 2 (age: younger versus older) $\times$ 2 (set size: five versus nine) analysis of variance, with repeated measures on the

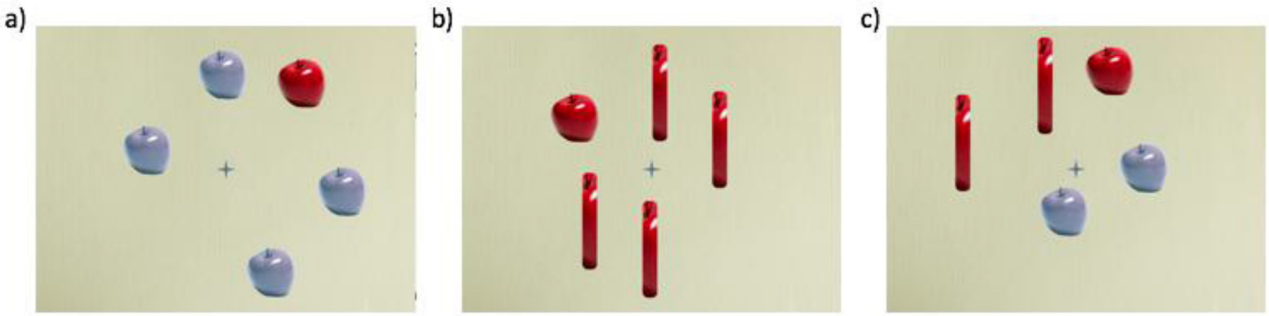

FIGURE. Illustration of the different trial types. In each trial, the target was a red apple. As soon as the child "found" the apple by looking directly at it, a reward was triggered. (a) shows single feature trials (shape only)—five objects; (b) shows single-feature trials (color only)—5 objects; (c) shows feature conjunction trials (color and shape). (The color version of this figure is available in the online edition.)

last factor. Age was dichotomized for these analyses using a median split (less than eight years versus eight or more years, for both groups). Outlying values were winsorized and RT data were $\log_{10}$ transformed for analysis to correct for positive skew. All effects were evaluated at a 0.05 level of significance; SPSS (v24) was used in all analyses; Bonferroni-adjusted significance tests were used for all pairwise comparisons. Finally, following Kaldy et al.,[18] single-feature and conjunction-feature conditions were analyzed separately.

We excluded from analysis trials with no looks to any items of the display (only 50 trials of the 1952 trials, 2.56%, were removed), and trials in which the child was looking to the target location at the outset (5.10% trials).

Quality of eye-tracking data

Recent work suggests that two aspects of the eye-tracking data, precision and robustness, could influence data quality, particularly look duration, and thus may need to be controlled.[20] Precision is compromised if the reporting of the position of gaze is inconsistent between samples. This happens when one of the elements (pupil, corneal reflection, and head position) is incorrectly and inconsistently identified by the eye-tracking software across different frames. Robustness is compromised when the tracker fails to report on position of gaze at all, leading the data to "flicker" off for periods. This can be caused by a number of factors, such as the corneal reflection becoming obscured by the eyelid because the child fidgets/moves. The child looking away from the screen can also contribute to low robustness. For calculation of these measures, see Wass et al.[20]

Results

Demographic and RSSS data

The final sample included 28 females with clinically diagnosed classical Rett syndrome ($M = 8.49$ years; $SD = 2.09$, and range = 2 to 12 years) and a comparison group of 32 typically developing females ($M = 7.71$ years; $SD = 2.87$, and range = 2 to 12 years); the groups did not differ in age, $t(58) = 1.05$. Data from six children with RTT were excluded either because of calibration problems (N = 3) or because they became overactive/restless during testing (N = 3); the clinical/background factors of those excluded did not differ from the rest of the sample.

Table 1 shows, for each child in the RTT group, their genetic mutation, age at test, and age at regression (all had completed active regression). The table also shows scores on the RSSS[19] and status on two subscales of the RSSS—walking and seizures. Composite scores on the RSSS averaged 8.11 ($SD = 2.23$); 41.4% of the children with RTT were ambulatory (walked unaided or with support), and 44.8% had a history of seizures.

Success rate

In the single-feature condition (Table 2), the overall mean success rate for children with RTT was considerably lower than that of the typically developing group: 48.7% (SD = 20.5) versus 83.6% (SD = 18.1), resulting in a highly significant main effect of Group, $F(1,56) = 52.02$, $P < 0.001$, $\eta_p^2 = 0.48$. There was also a significant Group × Set Size interaction, $F(1,56) = 6.02$, $P = 0.02$, $\eta_p^2 = .10$. Follow-up paired t tests, comparing performance on the two set sizes for each group separately, showed that performance of the typically developing children was influenced by set size, with success rates higher with the smaller 5-item arrays, $t(31) = 2.39$, $P = 0.03$ by contrast, performance of the RTT group was not significantly affected by set size $t(27) = -1.30$, $P = 0.20$. There was also marginally significant Group x Age interaction, $F(1,56) = 2.85$, $P < 0.10$, $\eta_p^2 = 0.05$, suggesting that age-related improvement was largely restricted to the typically developing group as well. Overall then, children with RTT were less successful than the typically developing group and, unlike them, their performance showed little evidence of being influenced by display size or age.

In the conjunction-feature condition (Table 2), the success rate of the RTT group was again markedly lower than that of the typically developing group, M = 42.0% (SD = 20.2) versus M = 77.9% (SD = 24.1), leading to a significant main effect of Group, $F(1,56) = 47.07$, $P < 0.001$, $\eta_p^2 = 0.46$. There was also a significant main effect for Age, $F(1,56) = 13.91$, $P < 0.001$, $\eta_p^2 = 0.20$, reflecting age-related improvement for both groups in this condition.

Latency to find the target

The mean RTs to find the target (on successful trials) are shown in Table 3. (Although RT measures were $\log_{10}$ transformed for analysis, the raw mean RTs are reported in the table for ease of understanding.) Analyses were done separately by condition; children were included in these analyses only if they had correct responses in both set sizes in the condition.

In the single-feature condition (Table 3), children with RTT took longer than the typically developing group to find the target, even when they were successful (averaging across age and set size, latencies were 1720 ms versus 1238 ms, respectively). This difference was reflected in a significant effect for Group, $F(1,40) = 4.33$, $P < 0.05$, $\eta_p^2 = 0.10$. None of the other effects were significant.

In the conjunction-feature condition (Table 3), while there was no main effect for Group, there was a significant effect for Set Size, $F(1,52) = 8.88$, $P < 0.01$, $\eta_p^2 = 0.15$, indicating that RTs slowed as set

TABLE 1.
Clinical and Genetic Characteristics of the Children with Rett Syndrome

Patient	Genetics	Age at Testing (years)	Age at Regression (months)	RSSS Total Score*	Ambulatory†	Seizures‡
1	R133C	8	15	8	0	0
2	R306C	11	18	5	1*	1
3	R133C	7	15	7	0	0
4	Large whole exon deletion	6	12	9	0	1
5	R270X	5	30	5	0	0
6	Deletion between exons 3 & 4	11	27	8	1*	0
7	Large whole exon deletion	9	18	6	0	1
8	R168X	7	15	9	1*	1
9	R255X	10	2	14	0	1
10	C916T	4	24	7	0	0
11	R168X	4	15	7	1	0
12	Deletion - heterozygous c.820_1193	11	18	6	0	3
13	T158M	12	12	11	1*	1
14	R168X	9	36	10	0	0
15	R294X	5	17	7	0	0
16	R168X	2	6	9	1	0
17	T158M	9	18	12	1*	1
18	Deletion	9	18	9	1*	1
19	R270X	7	12	10	0	0
20	R255X	8	12	6	0	0
21	C terminal deletion	8	30	7	1*	1
22	C terminal deletion	11	33	8	0	0
23	R168X	5	10	7	1*	1
24	P322S	12	15	5	1*	0
25	R168X	10	36	10	0	1
26	R294X	4	14	8	0	0
27	P152A	6	12	6	1*	0
28	P152R	11	12	11	0	1

* RSSS, the summary score of the expanded Rett Syndrome Severity Scale, comprises clinical ratings on seven parameters (seizure frequency/manageability, respiratory irregularities, scoliosis, ability to walk, hand use, speech, and sleep problems). Each parameter is rated on a four-point Likert scale from 0 (absent/normal) to 3 (severe).
† Walking: 0, no walking; 1, unsupported walking; 1*, walking with support.
‡ Seizures (subscale of RSSS): 0, absent; 1, mild; 2, moderate; and 3, severe.

size increased. There was also a significant interaction of Group × Age, $F(1,52) = 6.29$, $P = 0.01$, $\eta_p^2 = 0.11$. Follow-up t tests for each group separately revealed a significant effect of age for the typically developing group, with older children faster than the younger ones, $t(30) = 2.11$, $P < 0.05$; for children with RTT, the difference between age groups was not significant. Thus, this interaction was due to older, typically developing children being faster than their younger counterparts.

Co-varying measures of data quality

Although precision was similar for both groups, $t(58) = 1.47$, ns, robustness was poorer for the RTT group, as indicated by shorter average fragment durations ($M = 1.46$ seconds, $SD = 0.47$) than the typically developing group ($M = 2.36$ seconds, $SD = 1.24$), $t(58) = 3.66$, $P = 0.001$.

Because of the difference in robustness between the groups, analyses of the RT time data were redone, using ANCOVAs to covary robustness. As indicated below, the results were largely unaffected, indicating that differences in robustness, or fragment duration (flicker), did not affect the findings.

In the single-feature condition, there was, as in the original analysis, only a significant effect for Group, $F(1,39) = 2.78$, $P = 0.05$, $\eta_p^2 = 0.08$. In the conjoint-feature condition, there were, as in the original analyses, significant effects for Set Size, $F(1,51) = 6.89$, $P = 0.01$, $\eta_p^2 = 0.12$, and Group × Age, $F(1,51) = 5.94$, $P = 0.02$, $\eta_p^2 = 0.11$.

TABLE 2.
Accuracy (% Correct) in Single and Conjunction Feature Conditions

Group	Set size 5			Set size 9		
	n	*M*	*SD*	*n*	*M*	*SD*
Single-Feature Condition						
Rett syndrome						
Younger (2-7 years)	13	42.31	27.73	13	55.77	18.13
Older (8-12 years)	15	46.67	31.15	15	50.00	26.73
Typically developing						
Younger (2-7 years)	16	81.25	17.08	16	70.31	33.19
Older (8-12 years)	16	96.88	8.54	16	85.94	20.35
Conjunction-Feature Condition						
Rett syndrome						
Younger (2-7 years)	13	33.65	18.67	13	33.65	21.28
Older (8-12 years)	15	50.00	19.48	15	50.83	29.68
Typically developing						
Younger (2-7 years)	16	62.50	28.14	16	71.09	27.66
Older (8-12 years)	16	91.27	12.12	16	86.20	19.53

TABLE 3.
Latency (Saccadic Reaction Time, in msec) to Find the Target in Single and Conjunction Feature Conditions

Group	Set size 5			Set size 9		
	n	*M*	*SD*	*n*	*M*	*SD*
Single-Feature Condition						
Rett syndrome						
Younger (2-7 years)	8	1673	1090	8	1963	987
Older (8-12 years)	9	1489	1006	9	1754	867
Typically developing						
Younger (2-7 years)	13	1320	503	13	1448	868
Older (8-12 years)	14	1002	523	14	1180	738
Conjunction-Feature Condition						
Rett syndrome						
Younger (2-7 years)	10	1138	779	10	1559	913
Older (8-12 years)	14	1334	404	14	1764	512
Typically developing						
Younger (2-7 years)	16	1522	512	16	1496	519
Older (8-12 years)	16	1082	450	16	1325	574

In neither analysis was flicker, nor any of the interactions involving flicker, significant. Thus, differences in robustness did not account for the group differences in latency to find the target in either condition.

Clinical characteristics of the children with RTT and performance

None of the clinical characteristics of the RTT sample listed in Table 1 correlated significantly with any measure of performance.

Discussion

The present study is part of a series assessing different facets of attention in children with RTT.[8,15] Attention was singled out for examination because of its pivotal role in driving cognitive development and because atypicalities in this fundamental ability are found in many other developmental disorders.[10-14,21,22] To assess selective attention we used a visual search task, where the target differed from the distractors in either a "single feature" (color *or* shape) or in a "conjunction of features" (color *and* shape). We also used eye-tracking technology and a gaze-contingent design, where the child was rewarded when her gaze landed on the target (the target briefly became dynamic, whirling to an accompanying sound).

There were two notable findings. First, children with RTT had considerably greater difficulty finding the target than their typically developing counterparts. In both the single-feature and conjunction-feature conditions, the RTT group was successful on less than 50% of the trials. By contrast, children in the typically developing group were successful on around 80% of the trials in both conditions. The relative difference between groups remained even in the face of age-related improvement. That is, children with RTT showed no "catch-up" over age.

Second, even when children with RTT were successful in finding the target, they were slower to do so than their typically developing counterparts, although this difference in RT was restricted to the single-feature condition. It should be noted that set size had the expected, and typical, effect on RT for both groups. That is, the effects of set size were minimal in the single feature condition, which requires only preattentive processes, but pronounced in the conjunction feature condition, where the time needed for serial search tends to be closely titrated to the number of items that need to be scanned.

Importantly, two findings indicate that when slower latencies were seen in children with RTT, they were not due to poorer data quality. First, the precision of the recordings did not differ between groups, indicating that the eye tracker picked up the location of fixations equally well for the two groups. Second, while the data for the RTT group were less robust, as indicated by more "flicker," covarying this factor did not appreciably alter the results.

It is unclear what factors underlie the difficulties encountered by children with RTT, particularly in their success in finding the target. One possibility is that they have difficulty shifting and/or disengaging attention from the distractors. The capacity to flexibly switch attention has been found to be compromised in other neurodevelopmental disorders, particularly autism.[22-24] These studies examined disengagement using the "gap-overlap task," which compares shifting attention from a central to a peripheral target in a baseline condition, where the central target disappears as a peripheral one appears, with that in an overlap condition, where the central target remains visible and competes for attention. Children with autism, and those at-risk for autism, often have difficulty shifting attention to the peripheral target in the overlap condition, where the central target competes for attention, whereas children with RTT seem to have difficulty shifting attention even on baseline trials (in press).

Another possibility is that visual search is impaired in children with RTT because they have difficulty distributing their attention across the display. This restriction of gaze was evident in an earlier study[7] where children with RTT viewed faces and patterns. Here they tended to hone in on one part of the target while avoiding other parts. This was most starkly evident in examining faces, where they often ignored key areas, such as the mouth or eyes. Visual scanning strategies are known to become more systematic with age, with children becoming less likely to focus on only limited portions, and less likely to revisit the same areas.[25] Immature scanning patterns may have hampered the visual search of children with RTT.

A related, but as yet uninvestigated, possibility is that the efficient search in children with RTT is compromised by a tendency to focus on local, rather than global, features. While adults tend to show a global-to-local processing sequence,[26] processing more global aspects of the display before the featural, or "local" information, some children tend to focus more on local information.[27] If children with RTT have a predisposition to focus on local features, as their scanning patterns suggest, their rapidity in finding the target would likely be compromised.

Identifying the mechanisms that underlie the impaired visual search of children with RTT should be the focus of future work. One way such knowledge could be gained is by utilizing interventions that may ameliorate performance. Two techniques that have shown promise in this regard are systematic spotlighting of different parts of the display,[28] and training programs targeting multiple aspects of attention.[29,30] Both techniques are gaze-based and may prove useful for improving attention in Rett syndrome and facilitating cognitive growth.

There are two limitations to our study that should be noted. First, as common with rare disorders such as RTT, the sample was relatively small. Second, while we were successful in identifying attentional atypicalities in RTT at the group level, we do not yet know if eye-tracking tasks have the requisite sensitivity to be useful for characterizing performance at the individual level.

In conclusion, this work has led to new discoveries about selective attention in children with RTT. These children had considerable difficulty finding a target embedded among distractors not only in the conjoint-feature condition (where serial search is required) but even in the easier single-feature condition (where the target pops out). These findings, in conjunction with previous studies from our lab, not only show atypicalities of attention in those with RTT, but also underscore the utility of gaze-based tasks for assessing cognitive performance in this group.

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