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Original article

Challenges in evaluating the oculomotor function in individuals with Rett syndrome using electronystagmography

Laurèl H.M. de Breet [a,1,2], Gillian S. Townend [b,*,2], Leopold M.G. Curfs [b], Herman Kingma [c,d], Eric E.J. Smeets [b], Floor Lucieer [c], Josine Widdershoven [c], Raymond van de Berg [b,c,d]

[a] Faculty of Medicine, Maastricht University, Maastricht, the Netherlands
[b] Rett Expertise Center – Governor Kremers Center, Maastricht University Medical Center, Maastricht, the Netherlands
[c] Division of Balance Disorders, Department of Otorhinolaryngology and Head and Neck Surgery, Maastricht University Medical Center, Maastricht, Netherlands
[d] Faculty of Physics, Tomsk State University, Tomsk, Russia

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ABSTRACT

Background: Rett syndrome (RTT) is a neurological disorder characterized by a broad spectrum of symptoms. Communication is a major area of difficulty. Use of eye tracking technology offers a potentially effective method of communication when underpinned by intact oculomotor function. In this study, oculomotor function was assessed using electronystagmography (ENG). However, challenges were encountered when examining individuals with RTT.

Purpose: To improve oculomotor examination in individuals with RTT by evaluating the challenges encountered during ENG examination.

Material and methods: Oculomotor function was examined in 17 girls and young women with RTT and 16 typically developing (TD) individuals using ENG. Observational analysis of both performance and results indicated that challenges in examination were mainly related to quality of attention and quality of signals. Subsequently these outcome values were explored quantitatively according to percentage looking time for attention and drift for signal quality.

Results: A significantly reduced level of attention and suboptimal electrode signals were evident in the RTT group when compared with the TD group for all tests except torsion swing.

Conclusion: The challenges in testing confirm that regular oculomotor examination should be adjusted to meet the needs of individuals with RTT. It is hypothesized that the RTT group's higher quality of attention on the torsion swing can be explained by the more

* *Corresponding author*. Rett Expertise Center – GKC, Maastricht University Medical Center, Postbox 616, 6200 MD, Maastricht, the Netherlands.
E-mail addresses: l.debreet@zuyderland.nl (L.H.M. de Breet), g.townend@maastrichtuniversity.nl (G.S. Townend), leopold.curfs@maastrichtuniversity.nl (L.M.G. Curfs), herman.kingma@mumc.nl (H. Kingma), eric.smeets@mumc.nl (E.E.J. Smeets), f.lucieer@mumc.nl (F. Lucieer), josine.widdershoven@mumc.nl (J. Widdershoven), raymond.vande.berg@mumc.nl (R. van de Berg).
[1] Present address: Zuyderland Medical Center, Sittard-Geleen/Heerlen, The Netherlands.
[2] The first two authors were equally responsible for the work described in this paper.
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forceful vestibular rather than visual-ocular stimulus operating in this test. Suggested adaptations include reducing the number of electrodes, changing the picture stimuli and bringing them closer, performing observational assessments rather than ENG, and using virtual reality goggles.

1. Introduction

Rett Syndrome (RTT) is a rare neurological disorder almost exclusively affecting females. The syndrome is characterized by a broad clinical spectrum of signs and symptoms with an overall pattern of stagnation, regression and possible partial recovery.[1–3] Initially, children show a period of 6–18 months of seemingly normal development. Thereafter, an arrest occurs in their development followed by a progressive loss of acquired skills such as purposeful hand function and spoken language.[4] Further comorbidities include autonomic dysfunction, breathing irregularities, scoliosis, gastro-intestinal problems, reduced somatic growth, osteopenia, gait apraxia, and frequent seizures which may or may not be epileptic in origin.[4,5]

The investigation described in this paper is the second stage of a two-part study based upon the premise that girls with RTT communicate through eye movements.[6–8] Typically, individuals with RTT demonstrate a loss in ability to communicate through traditional means (e.g. speech, signing) but retain the ability to communicate through eye gaze or eye-pointing behavior. The use of eye tracking technologies to facilitate communication is increasingly promoted with this population.[9–11] In the first part of the study,[12] electronystagmography (ENG) was used to test the eye movements of girls with RTT. Saccades, smooth pursuit (SP) and optokinetic nystagmus (OKN)[13–15] were examined as indicators of oculomotor function while torsion swing (or the vestibular-ocular reflex (VOR)) was assessed as a measure of vestibular function because eye movements are closely related to the function of the vestibular organ. For all of these tests, attention is a particularly crucial element.

In recent years, a number of studies have explored aspects of attention in girls with RTT. Fabio et al.,[16,17] for example, have considered selective attention and evaluated the ability of individuals with RTT to look to a target object in preference to other non-target objects or faces (of assessor or caregiver). They also looked for evidence of joint attention behaviors, such as looking between target object and caregiver. Whilst identifying impairments in selective attention to target objects and a heightened interest in social stimuli, they also found that selective attention to objects could be improved through containment of hand stereotypies and through training. This, Fabio and colleagues concluded, had important implications for communication and cognitive functioning, as increases in distractibility and in responses to irrelevant stimuli interfered with processing of relevant information. Rose et al.[18–20] have also explored the selective attention of girls with RTT, as well as their ability to maintain attention. Their most recent study[20] lends support to the fact that individuals with RTT demonstrate impairments in selective attention, while their earlier studies[18,19] also show that they are capable of maintaining attention on a stimulus and can orient relatively quickly to the appearance of a target in the visual field. However, individuals with RTT demonstrate more difficulty with sustained attention when compared to a healthy control group,[18,21] and have been found to be slower to engage with moving objects, to be more distractible, and slower to re-engage.[18] Thus, attention can be divided into categories such as ‘selective’, ‘shifting’, ‘sustained’ and ‘joint’ attention, with selective being the ability to focus on the relevant or target stimuli, shifting being able to disengage at one location and re-engage attention at a new location, sustained attention being the ability to maintain focus over an extended period[19] and joint attention being able to share a point of common reference with another person. Shifting attention is of interest in the present study as it follows a saccadic pattern of eye movement. Shifts are reactive to external changes in the visual field when under exogenous control, for example, in response to a moving object.[19]

At the end of the first part of the study, it was concluded that the oculomotor function of individuals with RTT appeared to operate within normal limits.[12] While performing the ENG examinations, however, challenges arose with the quantitative data analysis as fluctuating and/or noisy signals were often encountered. It was hypothesized that these might be the result of a lack of attention and/or suboptimal quality of electrode signals, respectively. It is important to acknowledge these problems, since they should not be interpreted erroneously as a pathological finding, but rather as an artefact. The chief goal of this second part of the study, therefore, is to evaluate the occurrence of these artefacts in females with RTT when compared to healthy, typically developing children, and to propose possible solutions for obtaining more reliable and reproducible oculomotor results when assessing individuals with RTT.

2. Material and methods

The study was conducted as a collaborative venture between the Rett Expertise Centre Netherlands – GKC and the ENT Department at MUMC+. It was performed in accordance with institutional guidelines and the 1964 Declaration of Helsinki. Ethical approval for conducting oculomotor research with individuals with Rett syndrome was granted by the MUMC + Medical Ethics Research Committee (NL57673.068.16/

METC162027) and written informed consent was obtained from the participants/parents for use of their anonymized data.

2.1. Participants

Two groups of participants were recruited: (i) an experimental group who all had a clinical and genetic diagnosis of RTT, and (ii) a similarly-aged typically developing (TD) control group. The RTT cohort was recruited from inpatients undergoing three-day evaluation of brainstem functioning at the Pediatric Intensive Care Unit (PICU) of MUMC + whilst the controls were children of hospital employees, recruited as part of a separate study collecting normative ENG data for children and teenagers.

2.2. Procedure

Oculomotor and vestibular assessments were conducted using ENG, with data recorded in Kingslab Version 1.6.1 (© Maastricht University 2015). Participants were seated on a fixed chair in a semi-darkened room with electrodes placed around their eyes. For the RTT group, photographs of individual family members and images of animals were projected onto the wall in front of them. For the TD children, cartoon characters and images of animals were used. Each participant was required to follow the movements of the digital images with their eyes, without moving their head. If required, their head was held stationary by a parent. Minimal verbal instruction was given. Oculomotor movements were registered by the electrodes and transmitted to the computer via a transducer worn around the participant's neck.

The testing procedure began with calibration. The calibration routine was also repeated between tests if necessary, to obtain as reliable a calibration as possible for all four tests. Saccades, SP and OKN were tested and, finally, the torsion swing test was performed in complete darkness to assess VOR. Visual acuity was not assessed in this study. Further elaboration of these procedures can be found in the description of the first part of the study.[12]

2.3. Analysis

2.3.1. Observational analysis

Trained clinicians evaluated the quality of all measurements (calibration, saccades, SP, OKN and torsion swing test) using observational analysis. Of particular interest in this part of the study were the quality of the participants' attention and the quality of the signals. Outcome values were determined in consensus and quantitative analysis was then performed for each cohort.

2.3.2. Calibration and saccades

A valid saccadic eye movement was defined as an eye movement in the same direction as the moving image within a timeframe of <249 ms, maintaining fixation until the end of the saccadic stimulus.

Attention was measured as percentage looking time, according to the formula: (total valid saccadic eye movements made by participant/total saccadic stimuli) x 100%. One saccadic stimulus was defined as one movement of the stimulus from the left to the right, or vice versa. The quality of the signals was classified by the degrees of drift, which reflected the signal to noise ratio (SNR).[22–24] “Drift” referred to the number of degrees by which the signal fluctuated over time, in the absence of eye movements.[22,24] This was measured in degrees per second (°/s). Three groups were used to classify the quality: <2°/s, 2–5°/s and >5°/s.

2.3.3. Smooth pursuit

A valid pursuit eye movement was defined as an eye movement with its direction and phase corresponding to the SP stimulus. Fixation had to remain until the end of one cycle of stimulation. Blinks were not considered to be a loss of fixation.

Attention was measured as percentage looking time, by: (total valid cycles of pursuit eye movements made by participant/total cycles of SP stimulation) x 100%. One cycle of pursuit was defined as a movement starting at one side, moving fluently to the other side and back again. Quality of signals was measured in the same way as calibration and saccades.

2.3.4. OKN

OKN was defined as the presence of a nystagmus, in the opposite direction from the moving images.

Attention was measured as percentage looking time, this time according to: (total number of seconds looking at moving images on the screen/total number of seconds of moving images on the screen) x 100%. The exact timing of the change in direction of the nystagmus and the change in direction of the moving images had to coincide. The stimulus velocity was gradually built up to 48°/s. For stimuli below 10°/s the response is normally poor, so these data were excluded from analysis. Eye movements of a significantly higher slow component velocity (scv) (°/s) than the velocity of the images on the screen, as judged by a trained clinician, were considered to be an eye blink or another artefact. The quality of the signals was evaluated as “quantifiable” or “unquantifiable”. The signal was quantifiable if drift was less than 5°/s, and unquantifiable if the drift was 5°/s or more.

2.3.5. Torsion swing test

The torsion swing (or VOR) was defined as a cycle of consecutive nystagmuses in the same direction as the movement of the chair and head.

Attention was measured as percentage looking time, by: (total correct nystagmic responses per stimulus/total of stimuli) x 100%. A correct nystagmic response was defined as a nystagmic response in phase with the torsion swing head movement. A minimum response of 50% per stimulus was considered a positive response. The quality of the signals was evaluated as “quantifiable” or “unquantifiable”. Once again, the signal was quantifiable if the drift was less than 5°/s and unquantifiable if drift was above this.

2.3.6. Duration of each test

The duration of each test was based on the performance of the individual. In cases where attention was judged to be good (reflected by a high percentage of looking time) and high quality of signals (reflected by a low degree of drift) only a couple of stimuli were required before continuing to the next test. In cases of absent or poor attention during trials, more stimuli were required in order to get as representable and reproducible results as possible. The minimum and maximum number of stimuli were respectively 5 and 72 for calibration, 10 and 60 for the saccadic test, for the pursuits 4 and 13 respectively, for the OKN 42–102 seconds and for the torsion swing 7 to 11 half-way turns.

2.4. *Statistics*

The primary outcomes were quality of attention (measured in percentage looking time) and quality of signals (measured in drift) during testing of the oculomotor function in individuals with RTT. Percentage looking time was classified into 5 groups, with the first set at 0% and incremental band widths of 25% for each subsequent group. Data were analyzed using IBM SPSS Statistics V.24 (IBM Corporation, New York, United States of America). The Shapiro–Wilk test and histograms were used for tests of normality. Median age was calculated for both RTT and TD groups. A Pearson correlation test was performed to determine the correlation between age and attention in calibration, SP, saccades, OKN and torsion swing. The relationship between age and the outcome of the quality of signals was determined by a linear regression analysis. Medians were calculated for percentage looking time of each of the tests. To compare the RTT group and control group, the Mann–Whitney U-test was used for attention and Fisher's exact test was used for signals. A significance level of 0.05 was chosen to detect significant differences within and across groups.

3. Results

3.1. *Participants*

Seventeen girls and young women with a clinical diagnosis of RTT (median age 7.67 years; range 2.58–25.92; SD 6.636) were included in this second stage evaluation. Sixteen TD children (median age 7.125 years; range 3.58–18.58; SD 3.95) were also included.

No significant correlations were found between age and percentage looking time in either the RTT or TD groups for the calibration, saccades, SP, OKN and torsion swing tests. Furthermore, no relationship was found between age and signals in any tests apart from SP in the RTT group, where there was a positive correlation ($p = 0.032$ and $B = 0.522$).

3.2. *Number of tests*

Numbers of participants per test are shown in Table 1. Most participants underwent at least one trial of each test; on some occasions a measurement was repeated while on other occasions a test was omitted due to loss of cooperation or compliance from the participant.

3.3. *Observational analysis*

Observational analysis demonstrated that the challenges in testing the RTT group were mainly associated with poor attention and low quality of electrode signals. Poor attention was demonstrated by a low percentage of time looking at the wall. The low quality of electrode signals was illustrated by a high degree of drift. It was decided to quantify these findings.

3.4. *Attention*

Table 1 shows the quality of attention (in percentage looking time) across the different tests. The number of individuals and percentage of each group falling within each band is shown. A wide distribution for the RTT group is illustrated, while the TD group is largely represented in the top 2 bands (above 50% looking time). Fig. 1 presents more clearly the levels of attention between the groups. A higher percentage looking time in the TD group was found compared to the RTT group for calibration ($p = 0.001$, $U = 50.00$), SP ($p = 0.017$, $U = 73.50$), saccades ($p < 0.001$, $U = 32.50$) and OKN ($p < 0.001$, $U = 48.00$). No significant difference was found for torsion swing ($p = 0.144$, $U = 71.50$).

Table 1 – Time spent looking at the stimulus.

Group	Measurement	Time spend looking at the stimulus (%)					Median looking time (%) [IQR]	Total (N)
		0%	1–25%	26–50%	51–75%	>75%		
		% (N)	% (N)	% (N)	% (N)	% (N)		
RTT $n = 17$	Calibration	12 (2)[a]	35 (6)	24 (4)	–	29 (5)	35[b] [63]	17[c]
	Smooth pursuit	24 (4)	6 (1)	24 (4)	18 (3)	29 (5)	50 [83]	17
	Saccades	25 (4)	25 (4)	19 (3)	6 (1)	25 (4)	27 [74]	16
	OKN	6 (1)	19 (3)	6 (1)	35 (6)	35 (6)	70 [62]	17
	Torsion swing	8 (1)	–	17 (2)	17 (2)	58 (7)	87 [50]	12
TD $n = 16$	Calibration	–	–	–	25 (4)	75 (12)	89 [16]	16
	Smooth pursuit	–	6 (1)	6 (1)	25 (4)	63 (10)	91 [30]	16
	Saccades	–	–	–	7 (1)	93 (14)	89 [9]	15
	OKN	–	–	–	–	100 (16)	100 [0]	16
	Torsion swing			6 (1)	13 (2)	81 (13)	100 [12]	16

Note. RTT = Rett syndrome, TD = Typically developing, IQR = interquartile range.
[a] Percentage (%) and number of individuals (N) in each group within specified bandwidth.
[b] Median time spent looking at the stimulus, per group per test.
[c] Total number of participants per test.

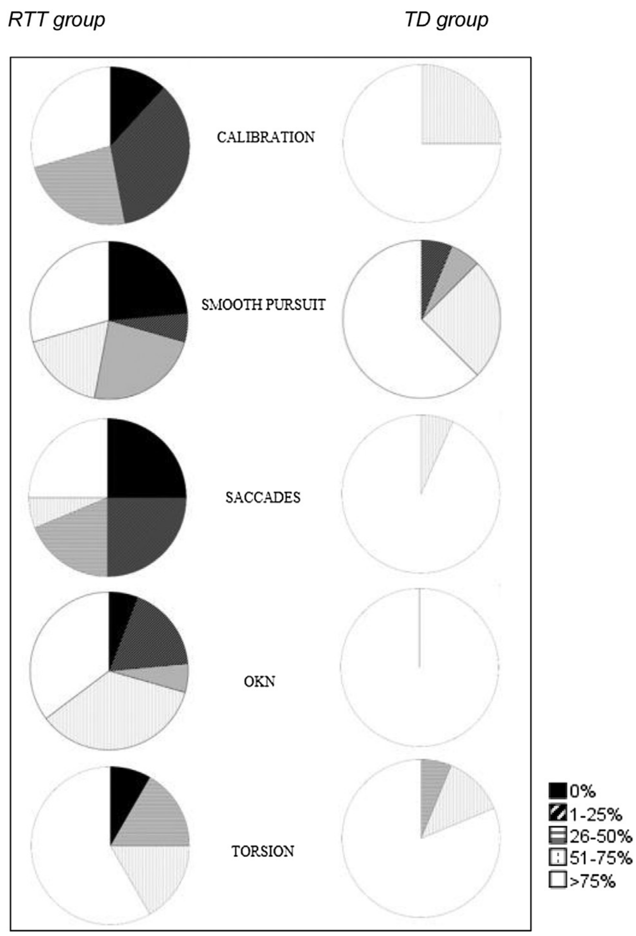

Fig. 1 – Quality of attention defined by percentage looking time for calibration, smooth pursuit, saccades, OKN and torsion swing. Note: Results for the RTT group are presented on the left of each figure, results for the TD group are on the right.

3.5. *Signals*

Tables 2 and 3 show the quality of the signals across the different tests, according to the degrees of drift. It is shown that the majority of trials for the RTT group were unquantifiable, while all results for the TD group were quantifiable, except for one outlier. Fig. 2 illustrates more clearly the comparison in quality of signals between the two groups. A statistically significant effect in quality between the RTT and TD group was found for calibration ($p < 0.001$), SP ($p < 0.001$), saccades ($p < 0.001$), OKN ($p < 0.001$) and torsion swing ($p = 0.004$).

4. Discussion

The evaluation reported here was designed as the second stage of a two-part study assessing oculomotor function in individuals with RTT,[12] after the first stage of assessment led to difficulties with the quantitative analysis of ENG results in individuals with RTT. Two main challenges were encountered: lack of attention and suboptimal electrode signals. Significantly more of these challenges were evident in the RTT group than in the TD group for all tests except torsion swing. It is hypothesized that the RTT group's higher quality of attention on the torsion swing can be explained by the more forceful vestibular rather than visual-ocular stimulus operating in this test. These challenges imply that regular oculomotor examination should be adjusted further to the needs of individuals with RTT.

4.1. *Quality of attention*

In recent years, several studies have shown that individuals with RTT have difficulty with both selective and sustained attention.[16–20] In order to counteract this, the ENG examination had already been adjusted to a certain extent. Firstly, tests were conducted more rapidly than usual, in order to reduce any loss of attention which might result from a sustained period of testing. Secondly, the examinations were performed in a minimally distracting environment: the room was dark and the technician and the parents were instructed to communicate as little as possible with each other and with the child.[25] Thirdly, the social preference noted in individuals with RTT was taken into consideration by utilizing portrait photographs of family members as stimuli during calibrations, saccadic and SP tests.[9,21,26] Nevertheless, attention remained an issue. One reason for poor attention could be related to the fact that the attention pathways are located in the frontal and parietal lobes. Since a significant decrease in the dendritic territories and afferent axons in the frontal cortices have been found in post-mortem brains of individuals with RTT, this could be part of the explanation.[27–29] In addition, anxiety and breathing irregularities are known to be major symptoms of RTT.[30,31] The unfamiliar situation associated with the examination, the darkened room, and episodes of hyperventilation and breath-holding during testing all appeared, on observation, to be factors interfering with the examination. A lack of interest/motivation in looking at the repeated stimulus may also have played a role. The photographs were small when projected onto the wall, and only 2–3 different photographs were used throughout the testing. The photographs could not be enlarged as it was necessary to stay focused on a specific point. From clinical observation, a better response was seen when a new and novel picture was introduced. This accords with the finding reported by Djukic et al., whereby individuals with RTT exhibited a preference for novel stimuli over a stimulus they had previously seen.[32]

4.2. *Quality of signals*

The other major challenge explored in this study was the quality of the signals. A drift of 5°/s or larger was deemed unquantifiable as normally-measured registrations of eye movements start at 5°/s.[23] Consequently, differentiation between a real eye movement and signal 'noise' is unreliable at or above this degree of drift. Amongst other things, poor signals were seen to be caused by poor head control and extraneous body movements relating to the dystonia and ataxia associated with RTT. While testing, a steady, fixed body

Table 2 – Quality of signals defined by the degrees of drift for calibration, smooth pursuit and saccades.

Group	Measurement	Classification of quality			Total (N)
		Unquantifiable	Quantifiable		
		>5°/s	2–5°/s	<2°/s	
		% (N)	% (N)	% (N)	
RTT $n = 17$	Calibration	65 (11)[a]	24 (4)	12 (2)	17
	Smooth pursuit	65 (11)	24 (4)	12 (2)	17
	Saccades	50 (8)	38 (6)	13 (2)	16
TD $n = 16$	Calibration	–	19 (3)	82 (13)	16
	Smooth pursuit	–	32 (5)	69 (11)	16
	Saccades	–	13 (2)	87 (13)	15

[a] Note. Percentage (%) and number of individuals (N) in each group by degrees of drift.

Table 3 – Quality of signals defined by the degrees of drift OKN and torsion swing.

Group	Measurement	Classification of quality		Total (N)
		Unquantifiable >5°/s	Quantifiable <5°/s	
		% (N)	% (N)	
RTT $n = 17$	OKN	60 (9)[a]	40 (6)	15
	Torsion swing	82 (8)	18 (2)	10
TD $n = 16$	OKN	–	100 (16)	16
	Torsion swing	6 (1)	94 (15)	16

[a] Note: Percentage (%) and number of individuals (N) in each group by degrees of drift.

position is necessary. Every movement, not just eye movements, is registered. In addition, it is hypothesized that the signals could have been better with more time. Achieving a good fixation of the electrodes and allowing time for them to set before they can be used for examination usually takes a couple of minutes. Placement was done more quickly with the RTT participants. After fixation, a poor calibration could also have been due to speed of testing, with faster and shorter episodes of testing leading to inaccuracy. Finally, it should be considered that the corneo-retinal potential of individuals with RTT may differ from other children/adults. Decreased neuronal function may result in a decreased corneo-retinal potential with decreased vision. Reports to date show no significant differences in *MECP2* levels or distribution in the eyes of patients with RTT[33] and no significant abnormalities in brainstem visual evoked potential (VEP) have been identified in studies of the innervation of the eyes.[34–36] However, the role of *MECP2* in the ocular pathway may be an area for further investigation.

4.3. *Limitations*

Analysis showed a variation in results, predominantly in the RTT group. This could be caused by a number of factors, including:

(i) The broad range of ages (2.58–25.92 for RTT and 3.58–18.58 for TD). Dividing into age groups was considered, but, due to the small sample size, this was not pursued as linear regression models showed that age had no statistically significant effect on test outcomes.

(ii) The different styles of digital image presented to each group during tests of SP and saccades – cartoon faces for the TD group (standard test presentation) and faces of close family members for the RTT cohort (adapted presentation). Both groups were exposed to the same images of animals for the test of OKN. As described above the use of adapted images for the RTT cohort was an attempt to appeal to their known social preference. However, in future assessments it would be better to use the same media across the two groups in order to remove another potential variable.

(iii) The different lengths of time the testing took. The selected time-span was determined for each individual by the assessing technician, based on the calibration and the individual's reaction at the start of the test. In normal circumstances, only a couple of cycles are needed to obtain a good overview and get a reliable result. Consequently, length of testing could be short if the start was good. In contrast, an absent response may have been recorded in the first trial, while a second trial with the same individual yielded a high percentage looking time. In such cases the absence of a response in the first trial could be due to the known delay caused by a-/dyspraxia in individuals with RTT.[37,38] Since all trial results were combined, the median percentage looking time was calculated per measurement. A delayed response could thus have interfered with the median percentage looking time.

(iv) Differing levels of visual acuity, which was not assessed. This is not routinely assessed during ENG as the test stimuli are considered to be of sufficient intensity and contrast to allow participants with reduced visual acuity

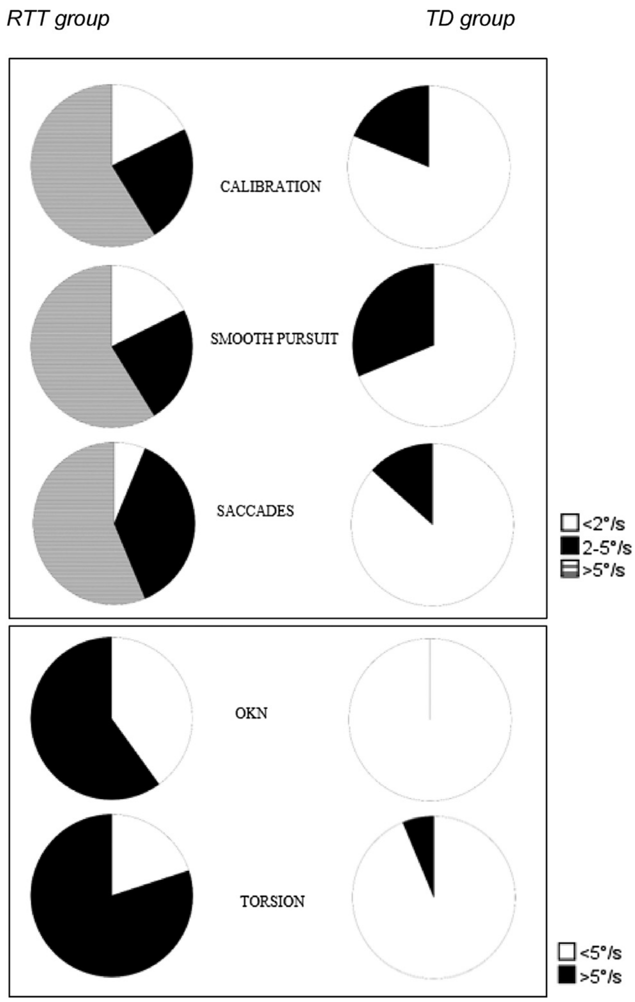

Fig. 2 – Quality of signals defined by drift for calibration, smooth pursuit, saccades, OKN and torsion swing. Note: Results for the RTT group are presented on the left of each figure, results for the TD group are on the right.

to see and respond to the target. Participants are also permitted to wear their glasses during testing.

(v) The effects of any breathing irregularities (e.g. hyperventilation and breath-holding) during testing. These were not systematically examined but would be a beneficial aspect to explore in the future.

4.4. *Suggestions for future research*

One simple suggestion for the immediate future, to achieve both better attention and better signals, would be to use fewer electrodes. From clinical experience, it is known that it is possible for the same ENG testing to be conducted with 3 electrodes rather than 9. In this case, two electrodes are temporal, since electrode fixation is better temporal than nasal, and one on the forehead serves as the earth or reference. Examination of vertical examination is no longer possible, but eye blinks, for example, can be identified by trained clinicians even in horizontal registrations. Secondly, the preference expressed by individuals with RTT for male caregivers, which is noted by some researchers [37], could be exploited in the examinations, by making sure only photos of familiar males are presented. This was trialed in some of the test cases, but was not structurally documented. A third option for examination could be simple observational testing of saccades, SP and OKN. The problems with the signals would thus be eliminated because ENG testing with electrodes would not be required. Observational testing was performed successfully with the TD group. An informal trial with one of the RTT group proved unsuccessful in a normal environment, however, this could be tested more formally with the RTT group in a distraction-free test environment. A fourth suggestion would be to project the images onto a computer screen immediately in front of the test subject, rather than onto a wall, bringing the images closer and in more immediate focus. In this case, however, the image would need to remain far enough away to prevent convergence. A fifth suggestion would be the use of virtual reality (VR) glasses. Through VR a more forceful stimulus is presented, as looking away is not an option. With these glasses, it is also possible to introduce stimuli which may be more appealing. However, the test subject would need to tolerate the glasses and the highly unusual environment, in addition to which using ENG to record the eye movements would mean that the issue of signal quality remains. Therefore, a sixth suggestion would be to use eye tracking glasses instead of electrodes. Virtual reality glasses combined with an eye tracker may thus be the final solution. This would potentially address both the attention and signal problems but would still require the test subject to tolerate the glasses. Currently such technology is under development and not widely available. For this reason, it is recommended that the other options suggested here are tried first. In the future, however, combined glasses could provide the ultimate solution for accurately examining oculomotor function in individuals with RTT if other ways continue to prove challenging.

5. Conclusion

A significantly reduced level of attention and suboptimal electrode signals were evident in the RTT group when compared with the TD group for all tests except torsion swing. It is hypothesized that the RTT group's higher quality of attention on the torsion swing can be explained by the more forceful vestibular rather than visual-ocular stimulus operating in this test. Overall, these challenges confirm that regular oculomotor examination should be adjusted further to meet the needs of patients with RTT. Possible solutions and adaptations are suggested.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2018.12.003.

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