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The use of virtual reality in Rett Syndrome rehabilitation to improve the learning motivation and upper limb motricity: A pilot study

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Abstract

The aims of the present pilot study were two: a) to investigate if learning and exercise in a virtual reality (VR) environment was motivating and emotionally positive for subjects with Rett Syndrome (RTT), and b) to examine if the speed of motor reaction was higher in a virtual or concrete environment. To achieve these aims, specific VR environments were developed to stimulate motor skills. Seven subjects with RTT were tested in three experimental conditions. In the concrete condition, real stimuli were placed on the table and the participants were invited to reach the stimulus. In the 2D and 3D conditions, a computer was placed on the table, and, through the developed software, stimuli were shown in 2D and 3D environments. The virtual system was able to recognize the reaching movements of participants. Thus, the object shown in the virtual environment moved towards the participant when the participant tried to grasp it. Results indicated that in the virtual environment the participants were more motivated and emotionally more involved in the proposed

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exercises. The motor speed was lower in concrete and 2D conditions than 3D conditions. This pilot study shows preliminary evidence on the usability of VR for RTT in improving learning, motivation and motricity.

Keywords: Virtual Realty; Rett Syndrome; General psychology; Motor abilities.

1. Introduction

Rett Syndrome (RTT) is a severe, neurodevelopmental disorder mainly caused by mutations in the *MECP2* gene, affecting around 1 in 10,000 female births (Amir, Van den Veyver, Wan, Tran, Francke, & Zoghbi, 1999; Amir & Zoghbi, 2000). Clinical manifestations include severe linguistic and motor impairments that are the core of phenotype symptoms. A patient with RTT initially appears to follow a typical development path, but at about 18 months of age a subtle regression in developmental acquisitions begins, opening the path to the clinical stages (Kaufmann, Johnston, & Blue, 2005; Pini, Bigoni, Engerström, Calabrese, Felloni, Scusa *et al.*, 2012). Loss of previously acquired language skills and of purposeful hand use, increasing difficulties in motor abilities (dyspraxia) and mental retardation, are the clearest signs of regression involved in RTT. Other typical signs of RTT include hand stereotypies, such as handwashing, handwringing, hand-mouthing, breathing disorders (holding breath and hyperventilation), ataxia, agnosia, bruxism, and epilepsy (Cuddapah, Robel, Watkins, & Sontheimer, 2014; Fabio, Martino, Caprì, Giacchero, Giannatiempo, La Briola *et al.*, 2018).

With reference to treatment for RTT, the literature shows that high frequency and low intensity rehabilitation leads to an improvement and to an increase in performance in all areas, from motor to cognitive aspects. Moreover, early and customized interventions are important to allow patients with RTT to reach their maximum potential, which is different for each case. The involvement and collaboration of families and caregivers in the treatment program is also essential (Fonzo, Sirico, & Corrado, 2020). Recent studies show that the association of traditional rehabilitation programs with new technologies, such as the use of a virtual reality (VR) tool, leads to the greater effectiveness of rehabilitation in participants with Neurodevelopmental Disorders (Tan, Dos Santos, Xiang, & Zhou, 2016; Damianidou, Arthur-Kelly, Lyons, & Wehmeyer, 2018; Fabio, Caprì, Colombo, & Mohammadhasani, 2022; Settimo, De Cola, Pironti, Muratore, Giambò, Alito *et al.*, 2023). VR allows inserting rehabilitation into a game environment, therefore increasing the participation of patients in rehabilitation programs not only in the short term but also in the long term (Kaplan, Cruit, Endsley, Beers, Sawyer, & Hancock, 2021). Mantovani and colleagues (Mantovani, Zucchella, Bottiroli, Federico, Giugno, Sandrini *et al.*, 2020) examined the key concepts that define VR: immersion (i.e., the extent to which the user perceives him/herself in the virtual environment rather than the real world), sense of presence (i.e., the subjective experience of the user of being in the virtual world), and the possibility to interact with the computer-generated environment. The use of VR in a clinical setting can have several advantages, which are described as follows (Mantovani *et al.*, 2020): it provides immediate feedback, it allows adaptation to the patient's performance, it is highly engaging, it has a high level of ecological validity, and can be combined with other tools/devices (e.g., electroencephalography, physiological activity registration tools). Moreover, the use of VR allows for a reproducible, objective assessment of cognitive processes underlying attention, memory, information processing, logical sequencing, and problem-solving (Zhang, Abreu, Masel, Scheibel, Christiansen, Huddleston *et al.*, 2001; Ventura, Brivio, Riva, & Baños, 2019). VR provides a safe, controlled environment to perform customizable, engaging rehabilitation activities that promote learning of both cognitive and motor skills (Aida, Chau, & Dunn, 2018). As regards research activity, VR provides a safe environment in which a researcher can assess skills that might be too dangerous or risky to perform in the real world and the tested participants can make mistakes without suffering from the real consequences (Zhang *et al.*, 2001).

However, the use of VR in rehabilitation of patients with RTT is still extremely limited (Lancioni, O'Reilly, Campodonico, & Mantini, 2001; Stasolla, Perilli, & Damiani, 2014). To be best of our knowledge, only one study (Mraz, Eisenberg, Diener, Amadio, Foreman, & Engsberg, 2016) reported the use of VR for rehabilitation purposes. This study was conducted on 6 patients with RTT, who were trained with online games using a MicrosoftKinect camera and FAAST software (Action and Articulated Skeleton Toolkit), which allowed to interact with the virtual game through body movements and without the need of cursors, remote controls, or controllers (Mraz *et al.*, 2016). Pre- and post-assessments were administered to examine any changes in upper extremity function. Each participant completed a VR test 3 times per week for 12 weeks, each session lasting 60 minutes. In the first session, the targeted movement was set as reaching forwards, requiring the extension of the elbow and the flexion/extension of the right arm’s shoulder. The movement threshold was set based on the participant’s range of motion. YouTube videos used during the intervention were chosen by the participant, who had to reach forwards to activate the YouTube video play mode. After approximately 10-15 seconds, the primary investigator or the caregiver would pause the video, requiring the participant to reach forwards to play the video again. Once a video was completed, the participant would point to the next video he/she wanted to play. The target movement was addressed as the participant progressed throughout the intervention to keep the activity a challenge. The forwards reaching target was kept the same, but the arm required for the task was switched to the left, forcing the participant to use his/her other upper extremity. Interviews and observation revealed successful game play when games were motivating, clearly established cause and effect and matched the level of cognitive ability of the participant. The VR intervention led to improvements in use of the upper extremities to complete self-care activities, an increased number of reaches completed in a 15-minute period, and a decreased time engaged in stereotypical hand movements.

Given that the use of VR-based interventions for motor rehabilitation in patients with RTT is limited, and, since VR has been demonstrated to be effective in the improvement of upper limb motor activity and functions of patients with neurological diseases (Georgiev, Georgieva, Gong, Nanjappan, & Georgiev, 2021), it becomes necessary to perform specific research with VR technological intervention for RTT. In addition, some research questions concerning the use of VR in RTT remain open: 1) can the learning and exercise in a VR environment be motivating and emotionally positive for patients with RTT? and 2) is the speed of motor reaction and activation of patients with RTT higher in a VR environment or a concrete environment? To answer these research questions, the main aim of the present pilot study was to develop a specific VR environment for patients with RTT to stimulate learning, motivation and motor skills and to compare it with concrete environments.

2. Methods

2.1. Participants

Seven girls with a diagnosis of RTT, ranging from age 5 to 38 years old (mean age 15.86 ± 11.27 years), were recruited from the Italian Rett Association (AIRETT). Patients with RTT were classified as clinical stage III (characterized by prominent hand apraxia/dyspraxia, preserved ambulation ability, and some communicative ability, mainly eye contact) or stage IV (late motor deterioration, with progressive loss of ambulation ability), according to the criteria for classic RTT by Hagberg and colleagues (Hagberg, Witt-Engerström, Opitz, & Reynolds, 1986). A general assessment was conducted by a psychologist before starting the experimental sessions, by using Downs' scale (Downs, Bebbington, Jacoby, Williams, Ghosh, Kaufmann *et al.*, 2010) to define the level of purposeful hand function as an evaluation of the functional level of the use of the hands, and by using the Rett Assessment Rating Scales (RARS; Fabio, Martinazzoli, & Antonietti, 2005) to evaluate the severity of the disease in patients with RTT. Table 1 shows the characteristics of the groups. The MECP2 mutation was seen in 100% of the sample; patients with the FOXG1 syndrome and CDKL5 disorder were excluded from the sample.

Table 1 – *Characteristics of participants*

Participants	Name	Clinical stage	Age	Level of severity (RARS)	Level of purposeful hand function (DOWNS' SCALE)
1	D.D.	IV	31	67.5	3
2	E.T.	IV	18	71	4
3	C.B.	III	5	85	2
4	E.B.	III	6	70.5	2
5	V.D.	III	7	64	2
6	D.B.	III	6	75	2
7	A.C.	IV	38	64	3

2.2. Measures

RARS (Fabio *et al.*, 2005) is a standardized scale used to evaluate the severity of the disease in patients with RTT. The total score allows to measure the severity of the disease along a continuum ranging from mild to severe symptoms. Skewness and kurtosis values in our data set, which were calculated for the distribution of the total score, were .110 and .352, respectively. Distribution was found to be normal. Cronbach's alpha was used to determine the internal consistency for the whole scale and subscales. Total alpha was .912, and the internal consistency of the sub-scales was high (from .811 to .934).

Downs' scale for the level of purposeful hand function (Downs *et al.*, 2010) is a scale that defines the level of motility of the hands of patients with RTT by assigning a score from 1, the minimum of manual functionality, to 8, the maximum of manual functionality; in particular the score is given as follows: 1) No observed hand function; 2) Able to hold at least one large object (cup, spoon, small ball or toy) >2s; 3) Need of assistance to grasp but able to pick up and hold at least one large object >2s; 4) Able to grasp, pick up, and hold at least one large object >2s; 5) Able to grasp, pick up, and hold at least one large object >2s and use a raking grasp to grasp, pick up and hold a small object (e.g. sultana, sweet, or small piece of sandwich) >2s; 6) Able to grasp, pick up, and hold at least one large object >2s and use the radial side of the hand to grasp, pick up, and hold a small object >2s (can be a pair of scissors, inferior pincer, or superior pincer grasp); 7) Skills for level 6 and able to transfer an object from one hand to the other (accurate pre-shaping of the hand is not seen); 8) Skills for level 7 and when hand is approaching an object, hand orientation and size recognition closely approximate the position and size of the object.

2.3. Parameters

2.3.1. Motivation Index (MI)

To assess motivation, we used a multiple parameter, defined as a “happiness index”. This parameter comes from the taxonomy of Van der Maat (1992), which is based on an extensive analysis of communication activity of people with deep intellectual disabilities with their usual caregivers (Petry & Maes, 2006). This taxonomy includes twelve main categories of behavioral form: (1) gaze direction, (2) facial expression, (3) sounds, (4) head posture, (5) head movement, (6) body posture, (7) movements of the lower limbs, (8) movements of the upper limbs, (9) mouth movements, (10) physiological reactions, (11) aggression and (12) conventional gestures. To create the multiple parameter, only five behaviors out of the twelve categories described were considered, i.e. gaze direction, sounds, mouth movements, physiological reactions (regarding the physiological reactions of the body, such as blushing or sweating) and hand gestures. They were recorded by a camera that was placed in front of the subjects during the three experimental conditions. Two independent blinded observers watched the video recordings and marked a cross on a checklist if the five behaviors were present/absent, assigning value 1 to “present” and value 0 to “absent”. The MI was defined as the sum of the score for each behavior. In this study, the agreement between the two independent blinded observers was 96%.

2.3.2. Coincident Timing (CT)

CT (Belisle, 2013; Fooken, Yeo, Pai, & Spering, 2016) is the parameter used to see the reaction times of the patient to the incoming stimuli recorded in tenths of a second. Coincident timing is defined as the perceptual motor ability to perform a motor response in synchrony with the arrival of an external object at a given point. This task uses a chronometer, which is displayed on the computer screen.

2.3.3. Length of reaching movement

The surface of the table is covered with graph paper. The participant's hand is placed on the lower edge of the table, which corresponds to distance 0. The computer and stimuli are arranged at a distance that corresponds to half the length of the participant's arm. The distance is measured in cm.

2.3.4. Retrieval Memory (RM)

Memory is evaluated at the end of the previous session (session 3), proposing the recognition of stimuli (presented for 3 times) and their discrimination from different distractions. Discrimination occurs between the concrete targets presented, between photos of the targets loaded on power points and between the three-dimensional representation of stimuli in the virtual room. The presentation is random.

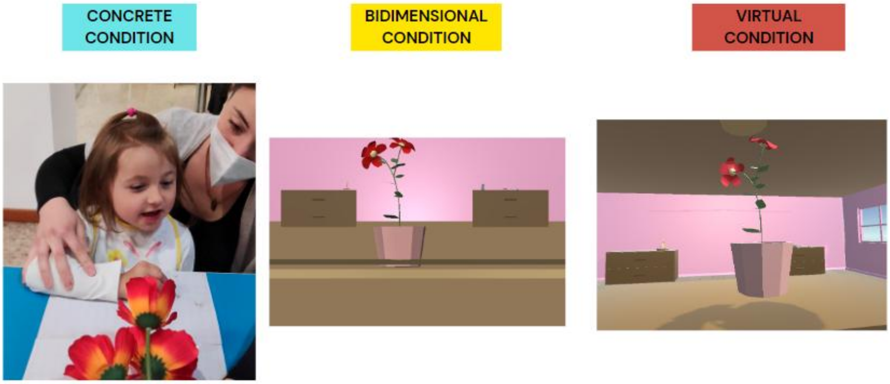
2.4. VR environment

A virtual system was created by AIRETT's engineering team. This system can detect the position of the body in real space and replicate it in the virtual world. In this way, the girl's movements are detected and then reproduced in a virtual context, resulting in an interaction with virtual objects. Artificial vision techniques are used to reconstruct a simplified version of the body (skeleton) and body movements are detected through a stereo camera to reconstruct them faithfully in a virtual space. To monitor the interaction between the girl and the virtual environment, AIRETT's team developed a Web application composed of three parts. First, a computer vision component was designed to be able to detect and represent the skeleton of the participant. The skeleton was further analyzed to recognize the reaching movement of the participant. This component was based on Google MediaPipe [https://arxiv.org/abs/1906.08172]. Second, a virtual environment that represented the scene in which the objects appeared, was implemented with Unity (unity.com). Third, an interface was designed to set the movement parameters, with respect to the physical conditions or preferences of the participant (e.g., the magnitude of the shoulder angle to activate the reaching movement, the choice between the left and right arm), or to choose an object that appeared in a scene from a list of objects, or finally to record the computer screen and, at the same time, the participant, for further analyses.

2.5. Stimuli

The reinforcing stimuli were a toy and a piece of food. The target stimuli, which the participants were familiar with, were a red ball and a bouquet of flowers. For each stimulus, a real object and its reconstruction in 2D and 3D, was used. Figure 1 shows an example of the images of the three experimental conditions.

Figure 1 – *Example of the three experimental conditions*



2.6. Procedure

Each participant went to the AIRETT Centre for 3 consecutive days in a week. Each session for each participant was videotaped with a front camera and a side camera positioned at 45 degrees and at a distance that framed the participant from head to toe. In all the experimental conditions, the sequence of sessions had the same structure, as follows: the participant was seated on her own orthopedic chair at a table with a central recess and that was adjustable in height (the height of the table was defined to ensure the elbow support of the dominant limb). The non-dominant limb was held under the table. For each session, a video recording of the patient was made for 1 minute in a neutral condition and in the absence of requests, to evaluate the motivation index before administration. The stimulus was thus presented to the participant and the therapist gave the following instruction "go get it". The therapist waited 1 minute so that the participant could start the body movement. If motor activation did not occur, the therapist repeated the verbal request, and the maximum range of time was set at 3 minutes, after which the stimulus was removed; the session was then considered finished for the specific stimulus. Stimuli were sequentially and randomly presented in the three conditions; the order of conditions was also varied between sessions. A break of two minutes was left between the three conditions.

In the concrete condition, real stimuli were placed on the table at the level of the midline. If the participant reached for the stimulus, the distance reached by the hand towards the target was marked on graph paper. In the 2D and 3D conditions, a computer was placed on the table and, through the software created by Airett engineers, stimuli were shown in 2D and 3D versions. When the participant reached for the stimulus shown on the screen, the virtual system was able to recognize the movement performed and the object shown in the virtual environment moved towards the participant as a feedback that it has been grasped.

3. Statistical analysis

The data was analyzed using the SPSS 24. The Shapiro-Wilk test was used to verify whether the distribution of the sample with respect to the dependent variables was normal. The results indicated that data was normally distributed ($p = .200$). Based on this outcome, analysis of variance (ANOVA) was performed assigning the type of experimental condition as the independent variable and the parameters as dependent variables. The Bonferroni correction was applied for multiple comparisons. Alpha level was set to $p < .05$ for all statistical tests. A Pearson's correlation analysis was performed to analyze the correlation between the MI and the dependent variables.

4. Results

Concerning the first aim of this pilot study, Table 2 shows the mean and standard deviation of the MI of participants in the three experimental conditions (concrete, 2D, 3D) in relation to the presented stimuli (ball, flowers, personal object, food). The experimental condition variable showed statistically significant effects ($F_{(2.12)} = 4.05$, $p < .04$), indicating that the different conditions in which the same stimuli were presented brought to differences in emotional reaction. As shown in Table 2, a high level of MI was reported in the 3D condition. The post hoc comparison also showed statistically significant differences between happiness in the 2D condition and 3D condition ($t(7) = 3.40$, $p < .014$). This indicates that participants showed more positive emotions in the virtual condition compared with concrete and 3D conditions.

Table 2 – *Mean and standard deviation of the Motivation Index of participants in the three experimental conditions*

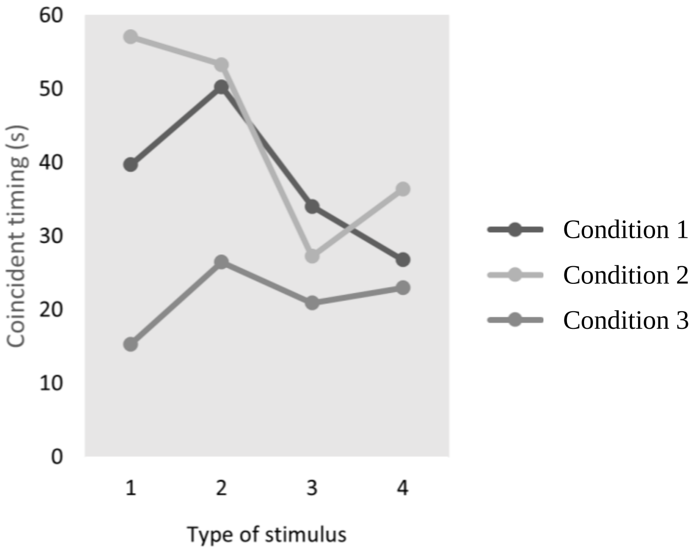
	Condition 1 (real condition)	Condition 2 (two-dimensional)	Condition 3 (three-dimensional)
Ball	17.38 (1.70)	15.07 (3.29)	18.11 (3.06)
Flowers	17.39 (1.71)	15.07 (3.31)	18.12 (3.02)
Favorite object	17.40 (1.73)	15.08 (3.31)	18.12 (3.02)
Food	17.45 (1.73)	15.09 (3.30)	18.13 (3.06)

Regarding the second aim of this pilot study, Table 3 shows the mean and standard deviation of the CT in the three experimental conditions (concrete, 2D, 3D) in relation to the presented stimuli (ball, flowers, personal object, food). Also in this case, the experimental condition variable showed statistically significant effects ($F_{(2.18)} = 18.07$, $p < .001$). The CT of all participants was higher in concrete and 2D conditions than 3D conditions, indicating that the participants were activated more quickly when stimuli were presented in the 3D condition (Fig. 2). The type of stimuli also showed significant effects ($F_{(3.36)} = 6.89$, $p < .003$). As shown in Figure 2, the participants showed a higher level of activation when their favorite objects were presented.

Table 3 – *Mean and standard deviation of the Coincident Timing of participants in the three experimental conditions in relation to the stimuli presented (ball, flowers, personal object and food)*

	Condition 1 (real condition)	Condition 2 (two-dimensional)	Condition 3 (three-dimensional)
Ball	39.73 (20.99)	57.07 (15.41)	15.33 (4.67)
Flowers	50.33 (27.46)	53.33 (17.30)	26.50 (2.02)
Favorite object	34.07 (11.17)	27.29 (16.60)	20.93 (7.11)
Food	26.80 (13.63)	36.38 (8.95)	23.00 (9.37)

Figure 2 – *Coincident Timing in the three experimental conditions*



Legend: black line = real condition; light grey line = 2D condition; dark grey line = 3D condition; 1 = ball, 2 = flowers, 3 = favorite object, 4 = food

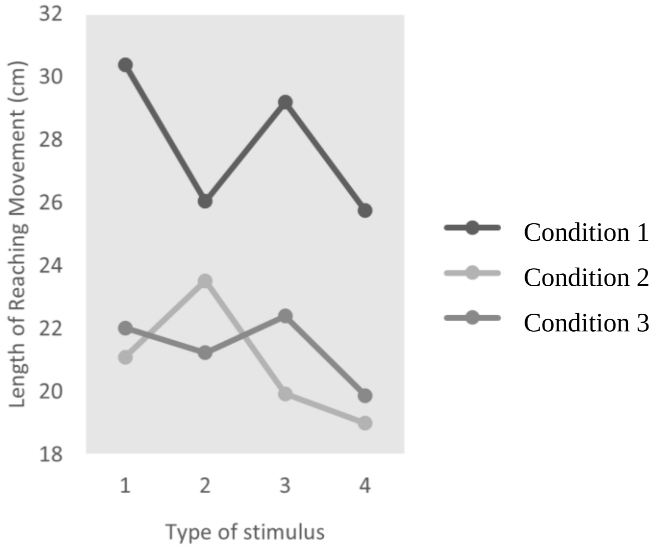
There was a significant interaction between experimental condition X type of stimuli ($F_{(6.36)} = 3.77$, $p < .005$), indicating that the participants increased their activation in the 3D condition rather than in the 2D and concrete conditions when every stimulus was presented.

Table 4 shows the mean and standard deviation of the Length of Reaching Movement parameter in the three experimental conditions in relation to the presented stimuli (ball, flowers, personal object, food). The experimental condition showed again significant effects ($F_{(2.18)} = 3.66$, $p < .05$). As shown in Figure 3, the range of the length of reaching movement was greater in the concrete condition than in both virtual conditions.

Table 4 – *Mean and standard deviation of the Length of Reaching Movement in the three experimental conditions in relation to the stimuli presented (ball, flowers, personal object and food)*

	Condition 1 (real condition)	Condition 2 (two-dimensional)	Condition 3 (three-dimensional)
Ball	30.39 (7.33)	21.10 (10.31)	22.02 (8.00)
Flower	26.05 (10.85)	23.52 (12.11)	21.24 (5.72)
Favorite object	29.19 (7.52)	19.93 (8.67)	22.40 (8.43)
Food	25.75 (6.90)	19.00 (7.27)	19.88 (7.66)

Figure 3 – *Length of Reaching Movement in the three experimental conditions*



Legend: black line = real condition; light grey line = 2D condition; dark grey line = 3D condition; 1 = ball, 2 = flowers, 3 = favorite object, 4 = food

Table 5 shows the mean and standard deviation of RM. No significant differences between performance in the three experimental conditions were found. This result is probably due to high variability, but trend data showed that participants remembered a greater number of targets in the 3D condition as opposed to the other two conditions (2D and concrete).

Table 5 – *Mean and standard deviation of Retrieval Memory in the three conditions*

	Condition 1 (real condition)	Condition 2 (two-dimensional)	Condition 3 (three-dimensional)
Retrieval Memory	2.57 (.78)	2.00 (1.00)	3.00 (.58)

A Pearson's correlation analysis was performed to analyze the correlation between the MI and the dependent variables. The results showed a positive and statistically significant correlation between MI in the concrete condition and the length of reaching movement in both the 2D and 3D conditions, respectively (r = .806, p = .05; r = .803, p = .05). There was also a positive statistically significant correlation between MI in the 2D and 3D conditions

($r = .819$, $p = .05$). Probably, these results can be related to the fact that the order of conditions was random between sessions and the MI was higher in the 3D condition.

5. Discussion

This pilot study investigated if learning and exercise in a VR environment was more motivating and emotionally positive for patients with RTT rather than in a concrete environment. Moreover, this pilot study was aimed at examining if the speed of motor reaction and activation of patients with RTT were higher in a virtual environment or in a concrete environment.

Comparing the emotional and motor activation in the three conditions, the results indicated that in the virtual environment the participants were more motivated and emotionally more involved in the exercises proposed. Moreover, the speed of motor performance was lower in concrete and 2D conditions than 3D conditions, indicating that the participants were activated more quickly when stimuli were presented in the 3D condition. However, the movement of reaching was greater in the concrete condition. This result was expected, as patients with RTT have always been trained to look and reach for a real object instead of just looking at the pictures on a screen, as in 2D and 3D conditions, so it is understandable that the reaching movement was greater in the concrete condition.

This pilot study shows preliminary evidence on the possibility of using VR for RTT in improving learning, motivation and upper limb motricity. However, future research with a larger sample size is needed to confirm the effects of VR on the use of the upper limbs in patients with RTT. Moreover, in this study, the virtual environment created was a realistic and very neutral environment to give prominence to the target to be reached; future research could create virtual environments, which are more animated and attractive from a multisensory point of view, inserting visual and sound animations to determine the level of VR intervention. Comparing the results of the present study with the work of Mraz and colleagues, it is possible to note that both studies demonstrated an understanding of the cause effect of motion and animation in the virtual environment (Mraz *et al.*, 2016). The study of Mraz and collaborators (2016) showed how the use of VR increased motivation and was able to qualitatively affect stereotypies at the level of the upper limbs. The present study showed how the virtual environment improved the times of activation and cognitive/motor attention during sessions in a virtual environment. These are fundamental prerequisites of motor rehabilitation in patients with RTT, as the dyspraxia component usually makes the beginning and maintenance of movement difficult, and stereotypies interrupt the sequencing of voluntary and controlled movement. Hence, both studies demonstrated the possibility of using VR in the rehabilitation of RTT, increasing target abilities and motivation.

The present research has some limitations that a pilot study can highlight. The results obtained cannot be generalized due to the small sample size, so we suggest caution in the interpretation of the results. However, RTT is a rare genetic disorder and it can be difficult to recruit a large data set with similar age or other features. Moreover, pilot studies are not a hypothesis testing study evaluating the efficacy of an intervention. They produce pilot date that can be used as a guide in the design and implementation of future larger scale efficacy studies (Leon, Davis, & Kraemer, 2011).

In conclusion, given the complexity of RTT as well as the limited state of knowledge concerning the methods to implement VR in patients with RTT, the present pilot study can be considered a significant phase of the research process suggesting that learning and exercise in a VR environment is more motivating and emotionally positive for patients with RTT rather than in a concrete environment. Hence, this pilot study is a necessary first step in exploring the use of VR as a novel and potential application of interventions in RTT and it offers support concerning the feasibility of use, considering the necessity of planning and of developing larger efficacy trial studies.

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